980

Division of
Research Resources

Program Highlights

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

1980

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Photo courtesy Illustration Services, University of California at Davis

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Introduction

Resources that can be shared by a broad group of biomedical scientists are vital to the development and practical application of new ideas in medicine and biotechnology. In addition, supplementary funds must be available to cover unexpected costs and to support unforeseen opportunities in research.

Through its five programs, the NIH Division of Research Resources (DRR) supports the development and maintenance of shared research resources—advanced tools, materials, and specialized environments for research—and locates them for maximum accessibility to biomedical scientists. Access to these cost-effective resources is critical to the continued quality of biomedical research, particularly in the current climate of reduced research budgets. The Division also supports expanded research capability for ethnic minority institutions, faculty, and students.

The Division currently supports 75 clinical research centers, 7 primate research centers, over 100 animal research resources, 43 biotechnology resources, and 79 minority biomedical support grantees. In addition, it provides funds to enhance the research capability of qualified research institutions and investigators through 506 Biomedical Research Support Grants.

The purpose of this publication is to describe the FY 1980 activities of each of the Division's programs and to highlight the resulting research progress in areas of national health concern.

READEX MICRO

Report of the Division Director

In FY 1980 the Division set the stage for the adjusting of research resource activities to the changing research requirements of the 1980's. These requirements were addressed in a set of planned actions outlined in the Division's 5-year plan (1982-1986), which was developed and published in 1980.

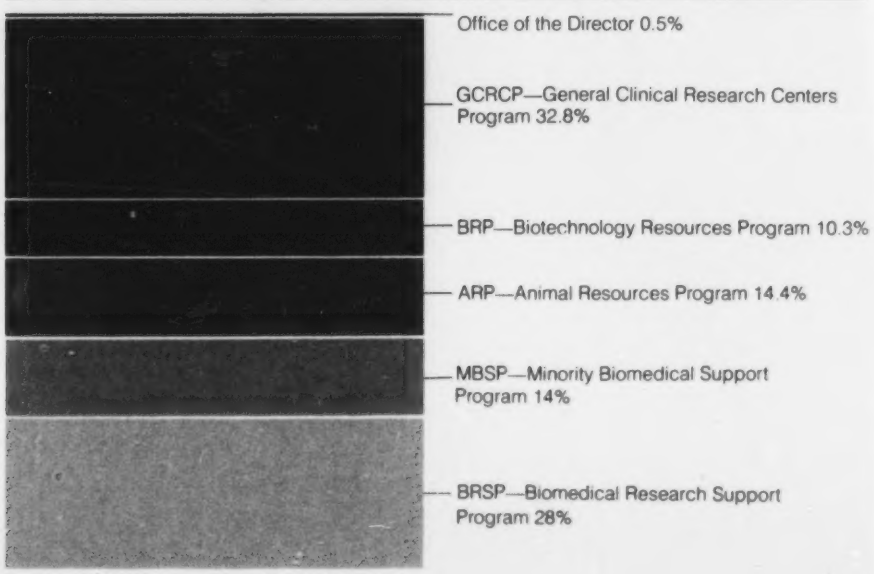
During the fiscal year, $163,063,000 worth of grants and contracts were made to 817 institutions. Seventy-five general clinical research centers (GCRC's) were supported, including 600 research beds and 75,000 outpatient visits. This support provided 80 percent of inpatient research care costs of NIH extramural research and helped to upgrade the centers' clinical data management capabilities and laboratory technology. The 43 biotechnology resources supported included large-scale minicomputer and microcomputer centers; facilities that house instruments such as mass spectrometers and million-volt electron microscopes for studying biological structure and function; and bioengineering facilities to develop such products as devices for measuring or imaging physiological processes in vivo.

Core support of 7 primate research centers enabled 138 center staff scientists to conduct research on 220 research projects, and provided 615 collaborative and affiliated scientists from various academic institutions with the opportunity to conduct primate research. Support for animal research and resource projects helped to bolster laboratory animal health, led to the development of animal models of human disease, improved facilities and equipment at animal resource institutions, and provided training in laboratory animal science.

In addition, the Division's Biomedical Research Support Grant (BRSG) Program awarded grants to 506 institutions to develop pilot projects, to purchase new equipment, to train new investigators, and to meet research needs not appropriately funded by Public Health Service (PHS) project grants or other sources. Through these awards, the BRSG Program directly supported approximately 10,000 research projects.

DRR Minority Biomedical Support (MBS) Program funds continued to upgrade the institutional research capabilities of MBS institutions and to increase the participation of minority faculty and students in biomedical research. MBS grants funded 79 institutions and positions for 1,030 undergraduates, 370 graduate students, and 660 faculty members.

FY 1980 Awards by DRR Components
Includes Research Grants, Research Training Grants, and R&D Contracts


Office of the Director 0.5%
GCRCP—General Clinical Research Centers Program 32.8%
BRP—Biotechnology Resources Program 10.3%
ARP—Animal Resources Program 14.4%
MBSP—Minority Biomedical Support Program 14%
BRSP—Biomedical Research Support Program 28%

By quickly adapting to meet the needs of biomedical researchers, the Division substantially strengthened their ability to develop ways to prevent, diagnose, and treat human disease. The following are a few of the many substances, techniques, devices, models, and treatments developed or tested using DRR-supported resources in FY 1980:

- ☐ Therapy for a group of fatal genetic diseases.
- ☐ Blood assay method to screen infants for cytomegalovirus infection.
- ☐ Computer system that models nerves in three dimensions.
- ☐ Battery-powered treatment of idiopathic scoliosis.
- ☐ Inflatable vest for cardiac diagnosis of children.
- ☐ Primate models for in vitro fertilization, atherosclerosis, and neonatal respiratory distress syndrome.
- ☐ Primate model for teaching communication skills to the handicapped.
- ☐ Potential vaccine against infectious mononucleosis.
- ☐ Laryngeal photography to aid the hearing impaired to speak more naturally.
- ☐ Potential vaccine for schistosomiasis.

The Division also accomplished the following important management and administrative goals set for FY 1980:

- ☐ Produced and distributed the Division's 5-year plan for 1982 to 1986.
- ☐ Expanded the DRR management information system to include subsystems for program-specific data and reports.
- ☐ Developed computerized capabilities to support the Division's budgeting process.
- ☐ Collected and analyzed all data from annual progress reports to answer the many NIH scientific inquiries received.

FY 1980 Overview of DRR Grant and R&D Contract Programs

Program	Appropriation	Major Resources Supported
General Clinical Research Centers Program	$ 56,335,000	• 75 General Clinical Research Centers • Over 3,000 Research Projects • 45 Clinical Associate Physicians
Biotechnology Resources Program	$ 16,754,000	• 43 Biotechnology Resources — 17 Computer Resources — 2 Biomedical Engineering Resources — 23 Instruments for Biological Structure and Function — 1 Cellular and Biochemical Material Resource
Animal Resources Program	$ 24,569,000	• 7 Primate Research Centers, including 220 Core Research Projects • 8 Primate Breeding Projects • 69 Animal Research and Resource Project Grants and Contracts • Training Programs
Biomedical Research Support Program	$ 47,516,000	• Biomedical Research Support Grants to 506 Institutions • 10,000 Pilot and Regular Research Projects • Central Resources • Development Awards to 30 Institutions
Minority Biomedical Support Program	$ 17,889,000	• 79 Institutions • 480 Research Projects • 660 Minority Faculty, 1,030 Undergraduates, and 370 Graduate Students • Minority Symposium
Office of the Director	$ 236,000	
Total Funding	$163,299,000	

- Provided computer simulation support to redesign the BRSG Program formula for allocating grants.
- Completed a 3-year audit of DRR position classifications.

In addition, the Division increased its response to the information needs and concerns of its biomedical research constituency and the lay public through its Research Resources Information Center (RRIC), contracted under the direction of the Division's Office of Science and Health Reports (OSHR). Through RRIC's award-winning *Research Resources Reporter* (circulation 17,000), the DRR informed researchers of the latest advances in biomedical research. The Division advised scientists where resources could be located for use in research through its revised directories of animal, biotechnology, and clinical resources, its directory of minority biomedical support institutions, and its new guide to BRSG grantees.

With OSHR assistance, the RRIC also published two special reports, *The Seeds of Artificial Intelligence: SUMEX-AIM*, and *Division of Research Resources 1979 Program Highlights*, and through Columbia University, produced a 15-minute film on the CARTOS neuron-tracing system developed at a DRR-supported computer resource facility. The film will be used as an instructional tool for presentations and exhibits and will be available to medical centers and other institutions. The outstanding quality of the Center's products was recognized by awards from the American Medical Writers Association, the Society for Technical Communication, and the National Association of Government Communicators.

The OSHR also organized and participated in numerous national, regional, and local communications projects to inform the public about research activities at DRR-supported facilities. At one GCRC, the Office developed and directed a "Health Science Tomorrow" lecture series targeted to the lay community. It placed many DRR stories in the national print media and arranged for guest appearances on TV and radio to inform the public of the importance of research resources. The OSHR also designed exhibits, produced a 10-minute film about research at the first dental GCRC, and managed the production of publications developed by DRR programs.

The OSHR, exclusive of RRIC activities, distributed 26,026 publications, received 14,835 mail requests, 385 telephone requests, and 85 walk-in requests, and responded to inquiries and requests from Congress.

Overall, the Division's achievements in FY 1980 reflect a judicious set of priorities for activities to meet the ever-changing research needs of the new decade.

James F. O'Donnell, Ph.D.
Acting Director, Division of Research Resources
National Institutes of Health

General Clinical Research Centers Program

Program Description

Today, at 75 general clinical research centers throughout the country, scientists study the entire spectrum of biomedicine from genetics to organ transplants. Researchers need the specialized facilities and expertise provided at these centers to study the biological processes underlying human disease and to test new diagnostic and therapeutic techniques. The regular hospital environment cannot provide this. Nor are laboratory or animal studies sufficient. Although some animals and in vitro models can simulate human biological systems and disorders, eventually it becomes necessary to submit procedures to clinical study. Moreover, a large number of human maladies exist only in man and cannot be modeled at all. Ultimately, there is no substitute for clinical research.

This realization led the U.S. Senate in 1959 to urge special studies on humans and to authorize establishment by the NIH of general clinical research centers. Eight centers were created in 1960 from a $3 million appropriation. The number of centers had grown to 60 when the NIH Division of Research Resources (then the Division of Research Facilities and Resources) assumed responsibility for the General Clinical Research Centers Program in 1962.

In the 1980's, the need for GCRC's will increase as researchers seek to ensure timely application of new biological and technological advances to human health problems. Recent breakthroughs in implantation therapy, recombinant DNA technology, and noninvasive imaging will require careful clinical evaluation to achieve their full potential to improve the nation's health.

To accomplish its objective of providing the specialized environment necessary for high-quality clinical research, the program currently supports, via competitive grants, 75 general clinical research centers. Each center is a miniature hospital-within-a-hospital with the specialized equipment and expert personnel necessary to provide a multidisciplinary, controlled research environment.

A GCRC functions as a discrete unit within a hospital. Most centers contain approximately 8 beds, but the range is from 3 to 30. Each GCRC contains a core laboratory, a metabolic kitchen, treatment rooms, a patient lounge area, a nurses' station, a conference room, and an outpatient section.

The combined inpatient capacity of the 75 centers is equivalent to that of a 600-bed hospital devoted entirely to clinical research. In addition to facilities for adult patients, GCRC's provide the unique care needed in pediatric studies. Currently, 88 of the research beds are on pediatric wards or in children's hospitals, and 70 of the centers admit pediatric patients on a regular basis.

Average GCRC (8.2 Beds) Funded in FY 1980

Personnel	Full-Time Positions	Dollars	Dollar Totals
Professional	1.2	$ 59,000	
Administrative	1.5	23,000	
Laboratory	2.6	42,000	
Dietary	3.2	42,000	
Nursing	12.9	204,000	
Other[1]	0.9	19,000	
Fringe Benefits		72,000	$461,000
Hospitalization			236,000
Travel			1,700
Supplies, Equipment, Other			35,000
Indirect Costs			49,000
Total Costs			$782,700

[1]Includes Clinical Associate Physicians

The combined inpatient capacity of the 75 GCRC's is equivalent to that of a 600-bed hospital devoted entirely to clinical research. Here, at one of the 70 centers that regularly admit pediatric patients, a researcher explores improved care for neonates at high risk of infection.

Program Highlights

During FY 1980 the program supported more than 3,000 inpatient and outpatient research projects at the centers. Other program accomplishments included upgrading the data management capabilities of several centers and enhancing the Clinical Associate Physicians (CAP) Program. Communication between centers was strengthened by a national meeting of GCRC administrative coordinators and a workshop for GCRC research nurses and dietitians. Finally, a 5-year plan for 1982 through 1986 was developed, reviewed, and published.

To upgrade data management capability, the GCRC Program installed the CLINFO clinical data management system at seven centers and held a meeting of system managers from the three prototype sites and the seven new sites so that the new managers could learn from the experienced group.

To attract more physicians to clinical research, two changes were made in the CAP Program, a postfellowship program intended to develop and retain clinical research talent. These changes included new allowance of $5,000 per year to each CAP for small equipment, supplies, computer time, and travel to scientific meetings (up to $800), in addition to the $30,000 yearly salary. Each grantee institution is now allowed a maximum of two CAP's. When there are separate adult and pediatric centers at a grantee institution, a maximum of three CAP's is allowed.

More than 3,000 research projects were conducted at the GCRC's in FY 1980, including research on diabetic retinopathy, a disease which impairs the vision of 46,000 diabetics each year. Magnification of a frog retina 3,400 times, shows the rods and cones (left) at their junction with the outer nuclear layer (right).

The more than 3,000 research projects conducted at the centers in FY 1980 were funded by the NIH and other agencies of the Department of Health and Human Services, by research foundations and societies, and by industry. GCRC support for these projects provided 80 percent of NIH extramural support for research patient care costs. Since 1970, GCRC research has expanded to include outpatient research, with an average of about 1,000 outpatient visits per center in FY 1980.

GCRC inpatient and outpatient research this year continued to reflect areas of national health concern: diabetes, genetic diseases, immune deficiency diseases, cancer, metabolic and hormonal disorders, infant health, alcoholism, and obesity. Results of some of these research projects follow.

Diabetes

Genetic Markers of Susceptibility. Researchers at one GCRC found that a gene in the part of the sixth chromosome called the major histocompatibility complex (MHC) or human leukocyte antigen (HLA) complex is associated with a high incidence of susceptibility to diabetes. While several genes are involved in diabetes susceptibility, this gene was found to be the best marker of the disease. While the finding provides no new evidence to explain the cause of diabetes, it does reinforce the current view that both genetic and environmental factors are involved in its development.

Improved Management of Diabetic Pregnancies. Diabetic pregnancies began to occur with increased frequency in the 1930's, when diabetic women treated with insulin survived to bear children. However, the mortality rate for infants of diabetic mothers was about 75 percent. GCRC research in recent years has improved management of these risky pregnancies and significantly reduced newborn mortality. Researchers at one

GCRC controlled the blood sugar of a group of expectant diabetic mothers with insulin, diet, and weekly checkups, thereby reducing the percentage of children born with defects of the heart, kidneys, and gastrointestinal tract.

Effect of Exercise on Diabetes. New data from a GCRC study indicate that physical training increases insulin binding and tissue sensitivity to insulin in proportion to the increase in physical fitness. The study suggests that a regular exercise program may have an important role in the management of insulin-resistant patients.

Genetic Diseases

Therapy for Group of Fatal Genetic Diseases. A research team at one GCRC developed and successfully tested a metabolic therapy that can control at least two of five hereditary diseases that shut down the urea cycle and lead to a deadly accumulation of nitrogen wastes, ornithine transcarbamoylase deficiency, and argininosuccinase deficiency. Through chemical stimulation of alternate metabolic pathways to dispose of nitrogen wastes, these wastes can be flushed out of the body before toxic levels are reached. This treatment, in combination with dietary management, has significantly extended the lives of affected infants and prevented the brain damage caused by accumulation of nitrogen waste.

Early Diagnosis of Cystic Fibrosis. Cystic fibrosis (CF), an inherited disease of children, adolescents, and young adults, affects 20,000 to 30,000 persons in the United States and occurs once in every 1,600 births. One effect of the disease is lung damage. A recent GCRC study revealed the extraordinary prevalence of hypogammaglobulinemia-G in young CF patients with relatively little lung damage. Immunoglobulin A (IgA) is low in these patients, whereas older CF patients have higher than normal levels of immunoglobulins. The researchers speculate that progression of lung disease in CF patients may in part be due to injury of lung tissue by a hyperimmune response, indicated by high levels of immunoglobulins. This new finding suggests that immunoglobulin levels may be used to diagnose the presence or the progress of cystic fibrosis.

Early Diagnosis of Hemochromatosis. Clinical investigation during 1980 resulted in an effective method for early detection of hereditary hemochromatosis, a frequently fatal iron-loading disease. Early detection is important since early therapy can prevent clinical manifestations such as liver and heart disease, hypogonadism, and skin pigmentation. The detection method includes HLA typing and iron-status tests of genotypic relatives to identify at an early age children who might have some biochemical expressions of the disease and those who are destined to become clinically affected.

Diseases of the Immune System

New Disease of White Blood Cells Discovered. A new disease of white blood cells, major defenders of the body against bacterial invaders, was discovered by a GCRC researcher this year. The disease cripples the white blood cell in its attempt to reach the site of infection and destroy disease-causing bacteria. It was discovered in a 5-year-old boy who had been referred to the center for a bacterial infection that would not heal in response to appropriate therapy. In his case, the unusual coexistence of a very high white count and a persistent infection suggested an abnormality in the function of the neutrophils, cells whose main function is to surround and kill invading bacteria. The researcher found that the boy's neutrophils lacked a glycoprotein present in normal individuals. Further investigation of his family revealed that the failure of neutrophil-spreading, and consequent ineffectiveness, was probably due to an inherited absence of this protein from the cell.

Synthetic Compound May Be Effective Against Multiple Sclerosis. A new synthetic compound tested at a GCRC shows promise as a treatment for multiple sclerosis (MS), an insidious disease in which the myelin sheath covering the nerves is damaged or destroyed. MS is thought to be caused by a virus that triggers an autoimmune response in which factors in the blood attack the myelin, resulting in dysfunction of the nerves and the subsequent symptoms of weakness, lack of coordination, motor reflex impairment, paresthesias, and visual and speech disturbances. It is currently treated with anti-inflammatory agents or immunosuppressants, which sometimes depress the immune system to a dangerous degree. Copolymer 1 does not impair the immune system, and in GCRC trials the compound resulted in improvement in some patients who had failed to respond to long-term treatment with immunosuppressant drugs.

DLE Treatment of Cellular Immunodeficiencies. Dramatic results were achieved at one GCRC with dialyzable leukocyte extracts (DLE) in the treatment of patients with severe cellular immunodeficiencies. The treatment group included individuals with a broad spectrum of immunodeficiencies; some were deficient in immune response to a single organism, some were suffering from types of cancer that are thought to be virus induced. Researchers at the center transferred dialyzed extract of white cells from normal donors

New treatments developed at a GCRC in FY 1980 prevent the deadly accumulation of nitrogen waste in newborns suffering from two hereditary urea cycle disorders. This treatment significantly extends the lives of affected newborns.

Photo by Gregory Freiherr

Micrograph courtesy Dr. Sergio Stagno

Electron micrograph of cytomegalovirus (CMV). A new blood assay method was developed at one GCRC to screen infants for CMV infection, which can lead to mental and physical retardation, sight problems, and immune system disorders.

to deficient recipients. This enabled the patients to produce mediators of cellular immunity, which protected them from further infectious attacks for about 6 months. Among the conditions that have responded favorably to DLE treatment are fungus infections, skin cancer, and tuberculosis.

Plasmaphoresis Treatment of Autoimmune Diseases. Plasmaphoresis was successfully used at one GCRC this year to treat Guillain-Barré syndrome, myasthenia gravis, and multiple sclerosis, three severe disorders in which the body becomes immune to its own tissues and attacks itself with antibodies, which are somehow triggered to destroy body cells or to block nerve-muscle communication. Plasmaphoresis, or plasma exchange, combats these diseases by removing the destructive antibodies from the blood. The blood is removed from the body, filtered, and replaced, minus the destructive antibodies. This treatment may relieve the often crippling effects of these diseases until they either remit spontaneously or are brought under control by drugs. It may also help patients who do not respond to drug treatment. In this particular study, the response to plasma exchange varied from dramatic improvement in some myasthenia gravis patients to only modest improvement in patients with multiple sclerosis.

Infant Health

Improved Diagnosis of Infant Epilepsy. Clinical researchers at one center developed a procedure to characterize infantile spasms, a serious disorder. The technique employs electromyograms, electro-oculograms, and electrocardiograms, and monitors respiration and skin electrical responses. These methods allow investigators to distinguish massive infantile spasms from other forms of epilepsy and from normal infant behavior. The

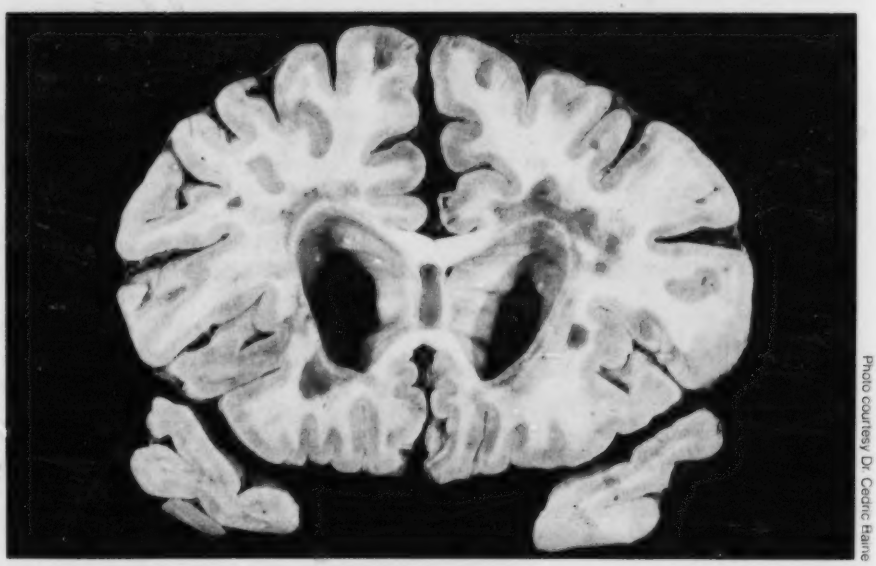


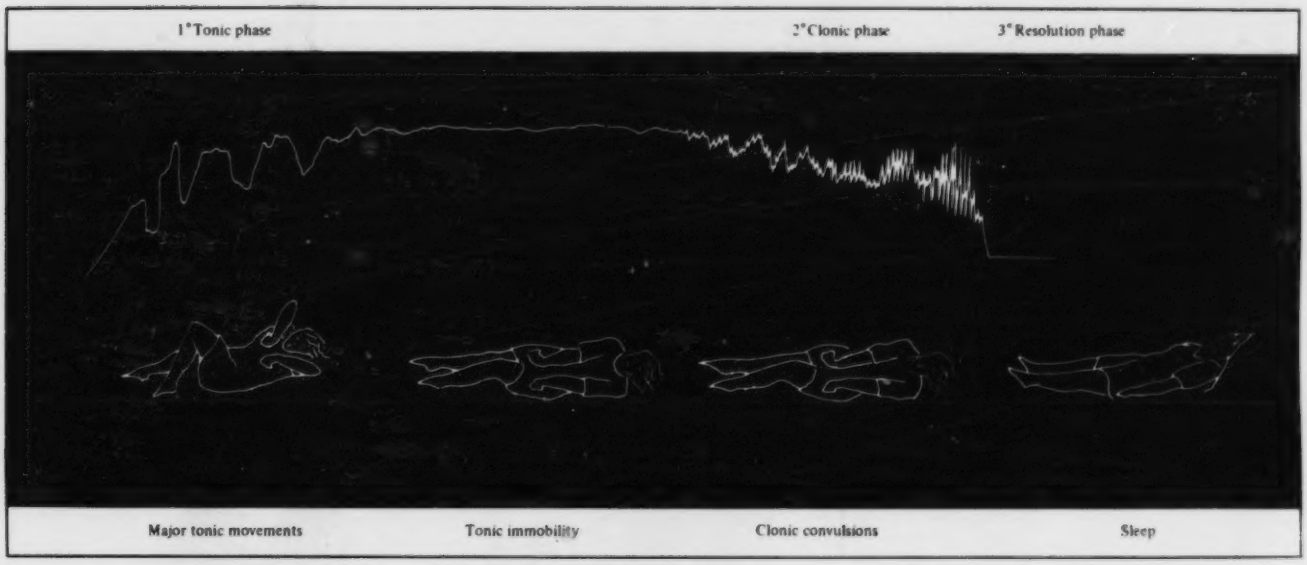
Photo courtesy Dr. Cedric Raine

GCRC investigators are studying a synthetic compound that may be effective against multiple sclerosis, an insidious disease in which the myelin sheath, or white matter covering the nerves, is damaged or destroyed. Damaged sections of the myelin (upper picture) are identified in gray areas of the illustration (below).

technique also allows the investigators to evaluate the efficacy of various drugs for treatment of this condition, including ACTH (adrenocorticotropic hormone) and a variety of cortisone-like compounds such as prednisone.

Improved Care of RDS Infants. Infants with respiratory distress syndrome (RDS) experience rapid fluctuation of oxygen levels. The oxygen balance must be stabilized within the normal range to avoid brain damage caused by low oxygen levels and blindness caused by high oxygen levels. A noninvasive, transcutaneous monitoring device developed by one GCRC team now provides immediate and continuous feedback on an infant's blood gases to the intensive care team. The device calculates oxygen levels in the blood by measuring the flow of oxygen through the skin. The transcutaneous method is safer than blood gas tests, which require drawing some of the infant's already limited supply of blood and may necessitate subsequent risky, invasive transfusions.

Screening for Infection That Causes Infant Hearing Loss. A new blood assay method was developed at a GCRC this year to screen infants for cytomegalovirus (CMV) infection, believed to be a leading cause in the United States of congenital hearing loss. Since the assay can be performed more quickly, conveniently, and inexpensively than previous tests, it may ultimately lead to wide-scale screening of infants for CMV infection in the future. CMV is a common cause of intrauterine infection and is often transmitted to the embryo during gestation. Largely asymptomatic in the newborn, congenital CMV infection may lead to mental and physical retardation, sight problems, and immune system disorders in addition to sensory neural damage resulting in deafness. Center researchers assayed each neonate's blood for RF antibody, which indicates the possible presence of CMV infection, rubella, syphilis, and a parasitic infection called toxoplasmosis. Positive RF tests were then confirmed with specific diagnostic tests. The new assay, which needs to be developed for greater sensitivity, identified 40 percent of the 1,500 infected infants in whom the disease had been diagnosed by conventional screening methods. Researchers are now working to increase the sensitivity of this test.



GCRC researchers have developed a monitoring technique to distinguish infantile spasms from other forms of epilepsy and from normal infant behavior. Here is a more primitive, late 19th century method to quantitate seizures by drawing patients' postures at various stages of a seizure on a split screen.

Metabolic and Hormonal Disorders

Potentials for Human Growth Hormone Treatment Are Broadened. Until recently, it was thought that only growth-hormone-deficient children could benefit from human growth hormone (hGH) treatment. The scarcity and expense of hGH, historically available only from the pituitaries of cadavers, severely limited the amount of research on other potential clinical uses. However, two developments during 1980 may substantially alter this field of research: findings at one GCRC that hGH can stimulate growth in short children not deficient in hGH, and the production of biologically active hGH by recombinant DNA technology. These developments may open exploration of possible clinical applications, ranging from correction of the short stature accompanying juvenile rheumatoid arthritis to more rapid repair of wounds, bones, and cartilage.

New Understanding of Menopausal Symptoms. GCRC findings that hot flashes experienced by postmenopausal women are associated with biochemical events in the brain, particularly sudden large releases of luteinizing hormone (LH) from the anterior pituitary, suggest a new approach to therapy. Research studies indicated that LH, or

Recent GCRC findings indicate that disconcerting hot flashes experienced by postmenopausal women are associated with sudden, large releases of lutenizing hormone (LH) from the anterior pituitary. Here, electrodes record changes in skin temperature and galvanic skin response after hot flashes.

more likely the factors that cause LH release, may trigger the hot flash. Perception of the hot flash results from a sudden shift of the body's thermostat by the brain. The subsequent symptoms of perspiration and flushing are automatic cooling mechanisms. The new therapy involves use of drugs called alpha-adrenergic inhibitors, which have been shown to block the release of LH in nonhuman primates.

New Nonsurgical Treatment of Pituitary Tumors. Research at a GCRC indicates that treatment with bromocriptine, an ergot alkaloid derivative, offers effective nonsurgical therapy for two disorders caused by very small pituitary tumors, hyperprolactinemia and acromegaly. In hyperprolactinemia, now known to be much more common than previously thought, an excessive secretion of the hormone prolactin causes abnormal lactation, loss of menses, and sterility. Bromocriptine lowers prolactin levels to normal and restores gonadal function. In acromegaly, the secretion of excess growth hormone causes coarsening of features, swelling of soft tissues, loss of gonadal function, and a tendency to diabetes. Bromocriptine helps reverse these abnormalities without adverse side effects.

Other Disorders

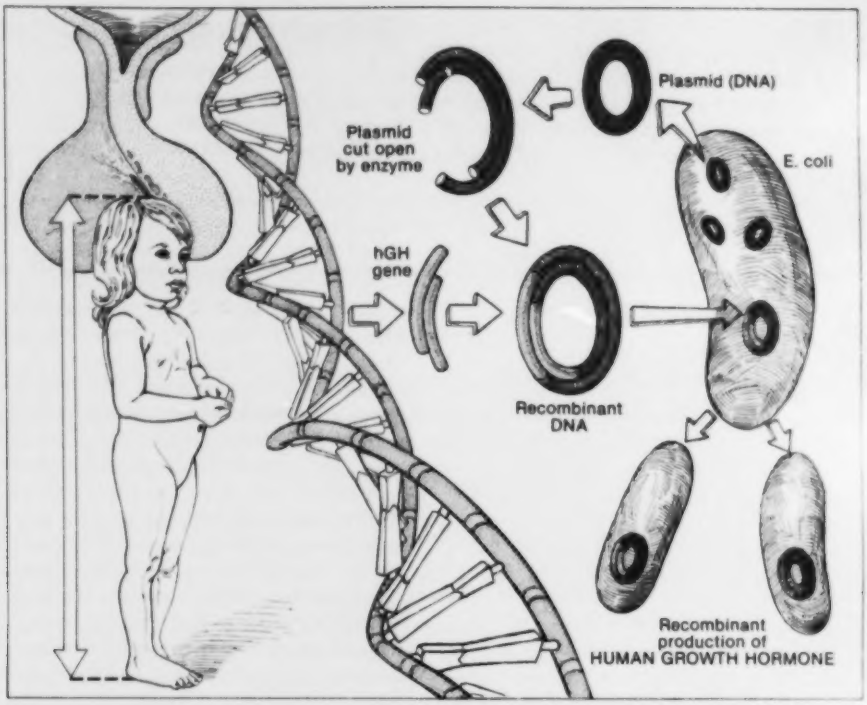
Enzyme Implicated in Obesity. A possible biochemical explanation was found by GCRC researchers for the tendency of people who lose weight to regain it. The enzyme lipoprotein lipase (LPL), which removes triglycerides from blood for storage in fat cells, was implicated. It increased to three or more times normal values in the fat cells of formerly obese people who had stabilized at a lower weight after stringent dieting. Enzyme levels seemed to remain high as long as weight remained low. This suggested that LPL may play some role in maintaining fat cell size even in the face of a diet that theoretically should not be sufficient for weight gain or fat storage. The study also suggested that LPL may be one of the links in a neuroendocrinological and biochemical mechanism by which the brain controls the number and size of fat cells, thus controlling the relative amount of body fat.

Multidisciplinary Treatment of Anorexia Nervosa. Recognition that a variety of factors—family interactions, biological mechanisms, and environmental stress—are associated with the onset of anorexia nervosa has resulted in multifaceted treatment approaches. Formerly, behavior modification, psychotherapy, or drugs were used separately as therapies for this still puzzling disease. By using a combination of nutritional rehabilitation, usually by behavior modification, and long-term family and individual therapy, some GCRC clinicians are now curing 80 percent of their patients. This comprehensive approach to treatment usually involves a team comprised of a psychiatrist, a social worker, a pediatrician (or internist), and nursing staff.

Woodcuts courtesy National Library of Medicine

Nineteenth century woodcuts illustrated the dramatic changes possible in a patient with anorexia nervosa (left), after successful treatment (right). A team of GCRC researchers have implicated family dynamics as a contributing cause of the illness. They combine family therapy with other treatments to achieve an 80 percent success rate with this complex disorder.

At one GCRC, research with human growth hormone (hGH) promises to expand the clinical uses of hGH to treat human growth disorders. Desire for timely application of such technological and biological advances as recombinant production of hGH will increase the need for GCRC facilities in the 1980's.



Future Program Directions

Investigators holding NIH research project grants or working on NIH center grants usually have adequate provisions for laboratory support, but they seldom have funding for the patient bed and clinical care costs. For example, investigators expected to use the centers in FY 1981 will have between $250 million and $300 million in support from other NIH grants and contracts, representing a large proportion of NIH extramural research on human subjects; however, fewer than 5 percent of these investigators will have hospitalization or patient care costs included in their NIH awards. These costs frequently cannot be borne by the subject of an investigation and will not be borne by hospitals or insurance carriers when research rather than treatment incurs the expense. Without access to facilities like the general clinical research centers, investigators would not be able to address the clinical application of laboratory findings.

To provide researchers with the needed facilities for clinical research in the 1980's, the program plans to maintain an adequate number of GCRC's. It also plans to maintain a skilled cadre of clinical investigators. Both goals have been identified as urgent needs and high priorities by the National Advisory Research Resources Council and the DRR during the next 5 years.

The GCRC Program has set the following specific program goals for the period from 1982 through 1986:

- ☐ Expand the number of outpatient facilities for multidisciplinary clinical research, place appropriate resource technologies and data management systems at the centers, and improve the conduct of GCRC clinical trials.
- ☐ Provide and maintain mechanisms for developing and supporting clinical research manpower.
- ☐ Establish administrative management objectives and follow-through for achieving greater intrainstitutional awareness of GCRC resources, increased intra-agency coordination with categorical institute programs, and improved operation and utilization of resources.

Biotechnology Resources Program

Program Description

As researchers delve into more minute levels of life, their understanding of biological structure and function becomes more sophisticated. Devices to image organs, cells, and molecules, to measure physiological processes in vivo, and to compute the resulting volumes of clinical data are essential to this delicate and intriguing research. Without these biotechnological tools, scientists often cannot advance in their investigations. For many, these instruments are the door from the unknown into the known.

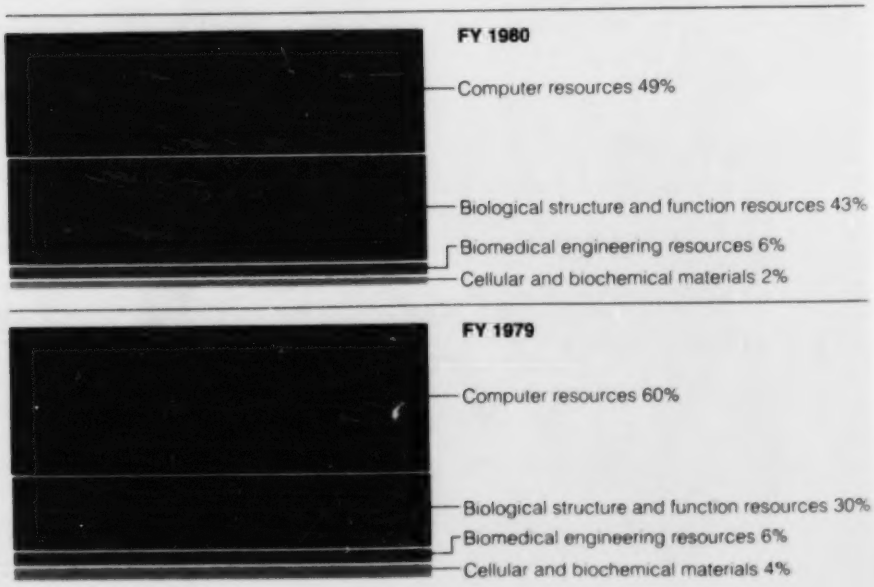
Biotechnological advances began to accelerate in 1962 when the NIH, at the suggestion of Congress, initiated a specialized research equipment program, now the DRR Biotechnology Resources Program (BRP). The purpose of the program is to support and develop technologies needed to solve biomedical and clinical research problems. Biotechnology resource facilities provide a unique opportunity for researchers to have access to specialized technologies necessary for their continuing investigations.

The three major types of resource facilities supported by the program are: specialized, large-scale, and mini- and microcomputer centers; bioengineering facilities that apply engineering and technology to develop biomedically useful products; and facilities that house instruments for analyzing and characterizing biological structure and function, e.g., mass spectrometers, million-volt electron microscopes, and nuclear magnetic and electron spin resonance spectrometers. The program provides grants and contracts for establishing, maintaining, and developing these resources and for adapting technological capabilities developed in the commercial sector for use by the biomedical community.

The program's main objective is to use specialized facilities and expertise in the physical sciences to create biomedically relevant technologies and to make these technologies accessible to biomedical scientists across the country.

Several of the resources are national in scope, and each is characterized by five specific research functions: core research, collaborative research, service, training, and information dissemination. Core research is conducted at the resource facility to develop and apply the technology. Often an on-site expert in the technology helps a user with a new and difficult application. Such collaborative research sometimes results in expanding not only the application of the technology, but also the depth of the research study.

Percentage of the DRR Biotechnology Resources Program Budget Funded for Each Type of Biotechnology Resource in FY 1980 Compared to FY 1979


FY 1980
Computer resources 49%
Biological structure and function resources 43%
Biomedical engineering resources 6%
Cellular and biochemical materials 2%
FY 1979
Computer resources 60%
Biological structure and function resources 30%
Biomedical engineering resources 6%
Cellular and biochemical materials 4%

By allowing a large group of investigators to share these expensive resources, the program has greatly reduced the national cost of biomedical research. Increased sharing of these resources has been achieved by placing them geographically according to national use patterns and by selecting for development those technologies most needed by NIH-supported and other U.S. biomedical research scientists. Use of the resources is encouraged by program-supported workshops and by program exhibits at scientific meetings.

Program-supported biotechnology was used during FY 1980 for research projects of several NIH institutes and of Public Health Service agencies such as the Alcohol, Drug Abuse, and Mental Health Administration, the Food and Drug Administration, and the Health Resources Administration. Originally supporting only large, general computer centers in medical schools, the program currently supports an extremely broad and innovative array of biomedically relevant technologies.

Program Highlights

In FY 1980 the program supported 39 resources and 4 resource-related research projects. The program funded four new resources, including a synchrotron radiation resource and a laser microbeam resource, offering specialized equipment and technology not available elsewhere on a shared basis. The synchrotron radiation resource was established for studies involving X-ray diffraction, X-ray spectroscopy, and fluorescence measurements. Initial research will characterize metal-containing proteins, using extended X-ray absorption, fine-structure techniques, and will determine protein crystal structures using anomalous X-ray-scattering information from single crystals. The former method takes advantage of the high intensity of synchrotron X-radiation, while the latter studies benefit from its tunable wavelength capability. The laser microbeam resource is the only shared resource of its kind in the country. It enables researchers to perform subcellular, cellular, and tissue-level microsurgery on cells either in vitro or in vivo.

The newly funded scanning transmission electron microscopy resource will be used to localize heavy-atom tags on proteins, nucleic acids, and cells. Applications of the newly funded clinical mass spectrometry resource will be in pharmacology and clinical medicine.

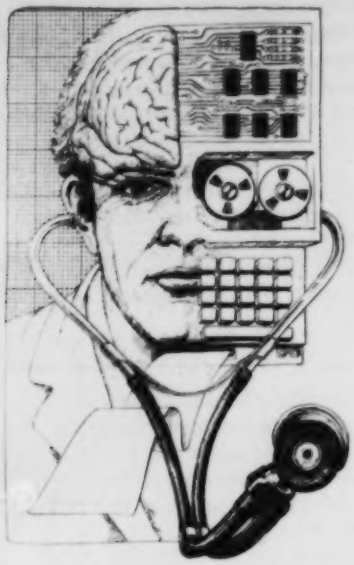
To encourage use of new and continuing resources and to educate potential users about state-of-the-art biotechnology, the program held six conferences or workshops in FY 1980 on the following topics: methods involving molecular structure in biological research; computer simulation resources; problems and opportunities of scanning transmission electron microscopy; implantable transducers and systems; the capabilities of 600 MHz NMR spectrometers; PROPHET; and artificial intelligence in medicine.

Two major program emphases in FY 1980 were development of noninvasive biomedical instruments and application of mini- and microcomputers to research and clinical problems. The following research highlights reflect the important impact of these and other technologies on advancing biomedical research.

Computer Resources

Today's DRR-supported computer systems are far more specialized, compact, and

Biotechnology resource facilities provide biomedical researchers with access to specialized technologies to further their investigations. Here, a researcher at a computer resource facility manipulates a three-dimensional computer image to examine a biological structure.



MYCIN, an offspring of the discipline of artificial intelligence (artist's depiction above), is an in-depth computerized base of medical knowledge of infectious diseases. It assists doctors in diagnosing infectious diseases and selecting appropriate therapy for individual patients.

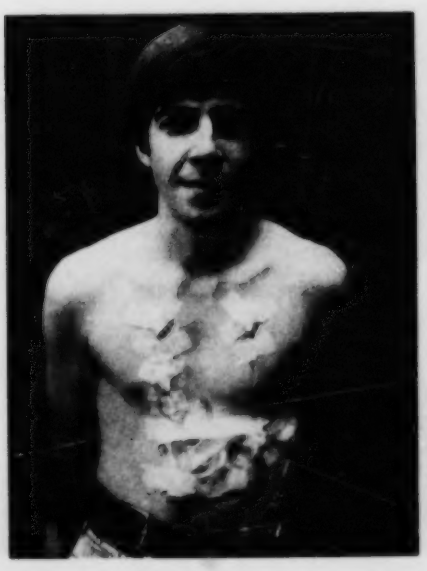
capable, yet less expensive to use than conventional computers. In addition to providing sophisticated numerical computing and information-processing services, present systems apply artificial intelligence methodology to clinical decisionmaking, interpret molecular structures, and image protein structures and nerve cells in three dimensions.

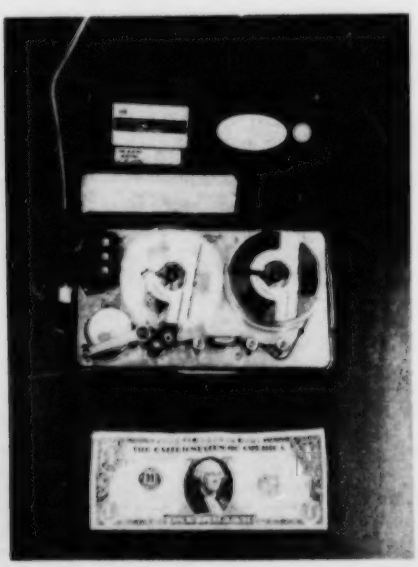
Color Computer Graphics Aid Drug Design. The ability to interpret drug action and design new drugs to fight disease has been greatly aided by the introduction of color to the computerized, three-dimensional, graphic display of molecules. Installed at a resource facility in the spring of 1980, this real-time interactive system enables researchers to study the complex interaction of large molecules such as proteins, hormones, and DNA, which comprise most drug receptors. Color coding permits researchers to observe where drugs bind to receptors, and thus to find lock-and-key relationships between drugs and their target sites in the body. With black-and-white graphic displays, researchers were limited to observing uncomplicated stick figures. Color systems enable researchers to comprehend much more complex pictures, observe the simulated interaction of two molecules, and distinguish active and inhibitor sites and interesting residues from the rest of the molecule.

CARTOS: Modeling Nerves in Three Dimensions. A new tool developed with program support enables researchers to see nervous systems at the most detailed level. To understand how human neurons branch and connect and how these patterns are altered by genetic and environmental factors, researchers developed a three-dimensional computerized system for modeling nervous systems with a technique called CARTOS, Computer-Aided Reconstruction by Tracing of Serial Sections. CARTOS can reconstruct complete models of simple nervous systems and partial models of larger systems. By studying the nerves of lower animals, researchers should be able to establish some basic rules of nerve structure, function, and development. These might eventually be applied to studies to illuminate complex functions and relationships of various regions of the human brain.

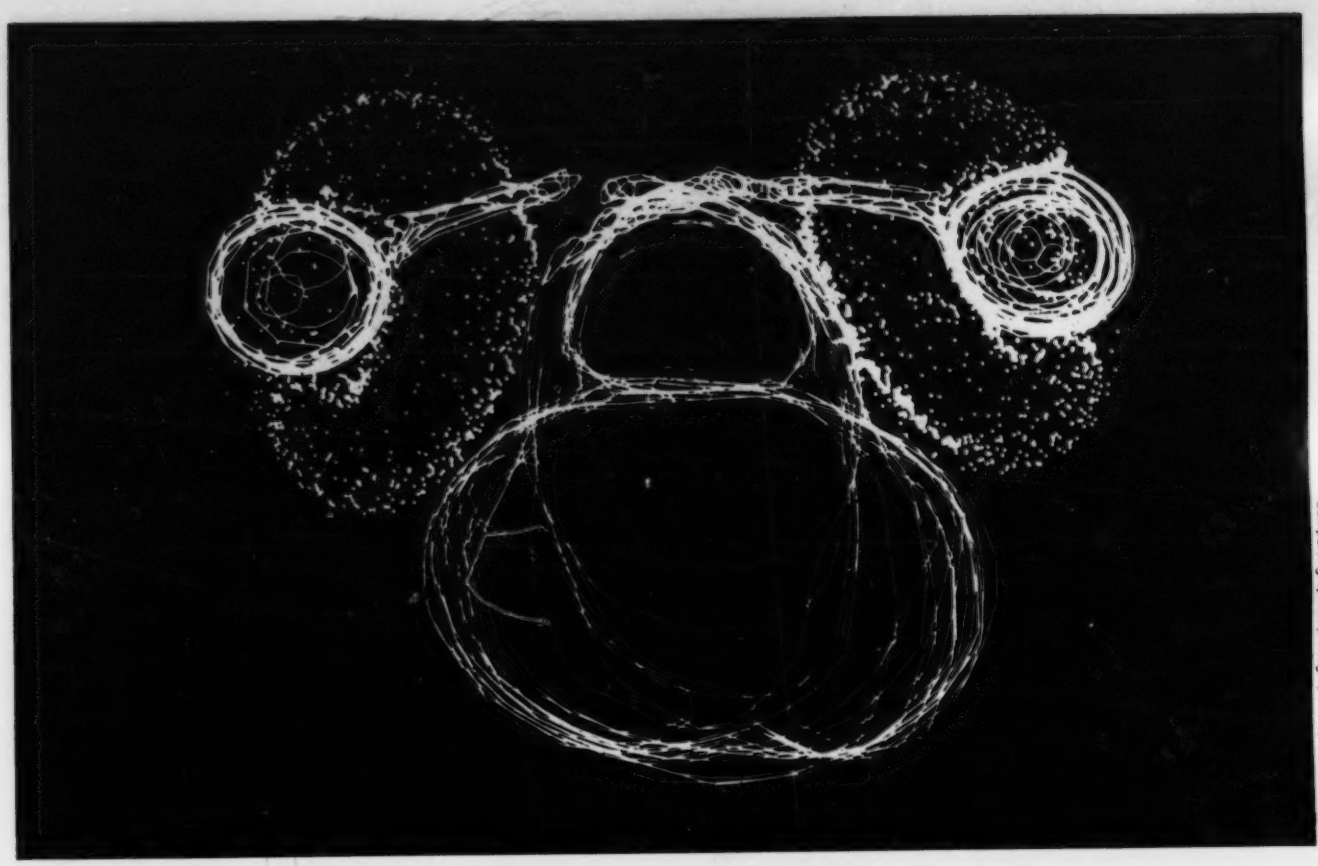
Argus Computer Aids Research Into Recurring Heart Attacks. A computerized system that interprets electrical signals of physiological phenomena may identify patients who are at high risk of sudden death from heart attack. Developed at a resource facility, the Argus/2H system relies on advanced digital computing techniques to analyze timing and waveform characteristics of heartbeats. The system is designed to identify heart dysrhythmias, which sometimes lead to sudden death in patients who have experienced previous heart attacks. Analyses of heart activity are entered in a central data bank along with other information, such as patient medical histories and demographics. It is hoped that these data will lead to criteria for identifying patients who are at high risk of experiencing another heart attack.

MYCIN: A Product of Artificial Intelligence. MYCIN is the offspring of a new field in computer science called artificial intelligence (AI), a discipline directed toward simulating the processes of human decisionmaking. The MYCIN program is a member of the Stanford University Medical Experimental Computer for Artificial Intelligence in Medicine (SUMEX-AIM), a DRR-supported national network of biomedical AI researchers that uses a central computing facility. Its objective is to assist physicians in diagnosing and treating





An Argus/2H system, which identifies life-threatening heart dysrhythmias, represents the research progress made possible with use of BRP-supported computer resources. Here, a lab technician demonstrates use of the Holter recorder, barely larger than a dollar bill, whose EKG tapes are analyzed by the high-speed Argus/2H computer system.



Computer graphics photographed by Nicholas Nectes

The brain, eyes, and optic nerves of a baby zebra fish as imaged by CARTOS, a computerized system for three-dimensional modeling of simple nervous systems. CARTOS was developed at a biotechnology resource facility as an aid to understanding how nerve cells are formed, how they function, and how they determine behavior.

patients with specific infectious diseases. The program is intended as a consultative aid to the nonspecialist, providing him with an in-depth knowledge base of infectious diseases. The knowledge base includes a logic scheme that allows the program to construct hypotheses and ask for such additional information as test results or observations about the patient's appearance. When recommending a diagnosis or therapy, MYCIN lists the rules and cites literature references used in the decisionmaking process. This explanatory function allows the physician to evaluate MYCIN's recommendation and make an informed decision to accept or reject the computer program's advice, or request further clarification of the rationale.

PUFF/VM. The Pulmonary Function Test Interpretation and Ventilator Management (PUFF/VM) project interprets standard laboratory measures of pulmonary function to present a tentative diagnosis of pulmonary disease for review by a physician. The BRP-supported computerized system measures pulmonary flow, lung volume, pulmonary diffusion capacity, and pulmonary mechanics. It then prepares a report for the patient's record, explaining the clinical significance of measured test results. The ventilation management (VM) program, still in early development stages, is being designed to interpret the clinical significance of physiological data from patients under intensive care.

Biomedical Engineering Resources

Biomedical engineering resources have increased in sophistication and range of application. One of the current foci of biomedical engineering is development of miniature sensors and implantable devices that enable researchers to measure chemical and physical occurrences in vivo. Another focus is electronic methods for diagnosing body conditions.

Tumor Temperature Sensor. The effectiveness of electromagnetic waves in reversing tumor growth by localized heating can now be measured by an implantable miniature thermometer array. Injected into living tissue by a hypodermic needle, the array monitors temperature at several points in the treated area to ensure that tumor cells are heated enough to be damaged, while healthy tissues are not overheated. Developed at a resource for silicon biomedical transducers, the thermometer array has already proved useful in short-term animal experiments.

Battery-Powered, Biofeedback Treatment of Idiopathic Scoliosis. Biofeedback techniques are being used by behavioral scientists at one biotechnology facility to treat

One of the current foci of biomedical engineering resources is development of miniature sensors and implantable devices, which enable researchers to measure chemical and physical occurrences in vivo. An implantable telemetry system receives and transmits data from sensors that monitor body temperature or bioelectrical activity.

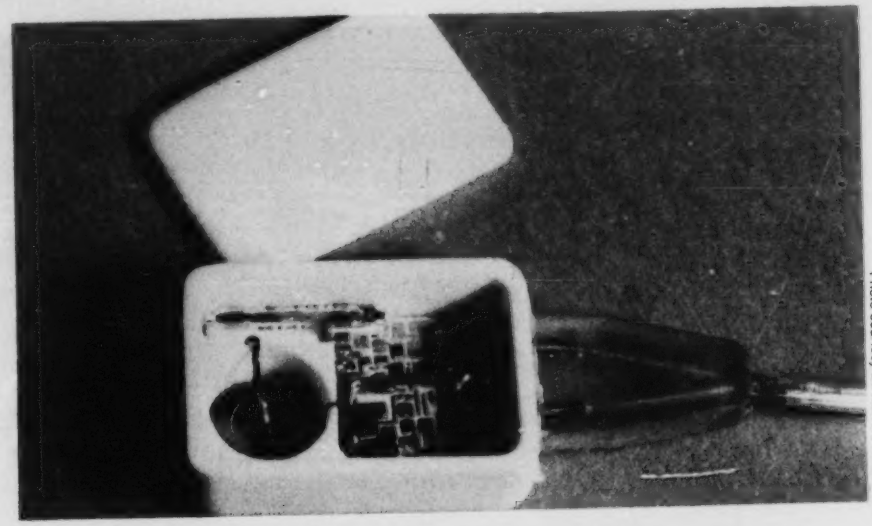


Photo courtesy Dr. Michael Neuman

idiopathic scoliosis, a lateral curvature of the spine. Scoliosis is usually treated by surgery or by a cumbersome and movement-restricting Milwaukee brace. With the new method, patients wear a small, lightweight, battery-powered device that detects undesirable posture shifts by means of two flexible bands placed about the torso. A miniaturized electronic circuit uses digital logic to respond to these postural shifts. After a prespecified time delay, an audio oscillator is turned on at low volume so that a faint tone is heard by the patient, signaling the patient to assume a correct posture. Once the posture is corrected the oscillator automatically turns off. Failure to correct the postural shift within a certain time results in a much louder oscillator tone. Results so far are encouraging: several patients have been able to slow down or arrest the increase in lateral curvature.

Body Surface Mapping for Cardiac Diagnosis of Children. An inflatable vest for measuring cardiac signals has been developed at a biomedical electronics facility. The electronic vest obtains surface potential signals across the dorsal surface and can be operated by a nurse to make cardiac recordings on magnetic tapes. The objective is to correlate body surface potentials with cardiac physiology and pathology in pediatric patients undergoing cardiac catheterization and in healthy children to obtain a data base on normal and abnormal patients. It is anticipated that this technique will prove superior to conventional cardiography and will have a great impact on determining the nature and treatment of cardiac disease, especially in children.

Instruments for the Study of Biological Structure and Function

New Applications of NMR Spectrometry. Nuclear magnetic resonance (NMR) spectrometry is a powerful investigative tool whose new applications were supported by the program this year. NMR analyzes molecular structure by placing atomic nuclei in a strong, uniform magnetic field and exposing them to a radio signal tuned to a precise frequency. The nuclei absorb and re-emit the radio signal. The strength of the signal received is in proportion to the number of nuclei present and thus indicates the chemical structure of a sample. Experiments with NMR have revealed important information on the structure and function of such complex molecules as hemoglobin and transfer RNA. By using specialized radiofrequency pulse techniques, it is possible to manipulate the magnetic interactions of atomic nuclei in solid samples. Recent applications of this method include studies of cholesterol in phospholipid membranes and of sickle cell hemoglobin in the gel state. NMR has also been used to study the active sites of enzymes, the interaction mechanisms between enzymes and inhibitors, the structure of various biomolecules, and mechanisms of protein folding and synthesis. Recent advances in scanning transmission electron microscopy (STEM) have allowed the examination of specimens at the atomic level. STEM engineers have developed a cold stage to minimize mass loss during measurement, a freeze-drying and vacuum-transfer system to avoid staining artifacts, and a data acquisition and analysis system optimized for quantitative mass measurements.

Production of Stable Isotopes for Research. This year a resource facility completed a 700-foot-long distillation plant for the enrichment of stable isotope carbon-13. The isotope will be distilled from its natural abundance level of 1.1 percent to an isotopic purity greater than 99 percent by the low-temperature distillation of carbon dioxide. This new plant will enable the routine production of all stable isotopes of the key elements in living

Biofeedback techniques have been used to treat idiopathic scoliosis, or curvature of the spine. With the new method, patients can wear a small, lightweight, battery-powered device instead of the conventional, cumbersome Milwaukee brace.

Drawing courtesy Scoliosis Research Society and Science News

systems. The isotopes can then be incorporated into natural products and drugs for research uses, such as metabolic studies for the early detection of disease, pharmacokinetic and bioavailability studies of drugs, and structural investigations of enzymes.

Mass Measurement of Small Particles. A scanning transmission electron microscope (STEM) resource developed the capability for accurate mass measurement of small particles visible to the electron microscope. This new technique will enable researchers to determine the number of subunits in the active complex of an enzyme such as biotin. The technique takes advantage of the linear relationship between the electron-scattering power of the specimen and its molecular weight. The STEM uses a cold stage to minimize mass loss during measurement, a system to freeze-dry and vacuum-transfer specimens, and a data acquisition and analysis optimized for quantitative mass measurements.

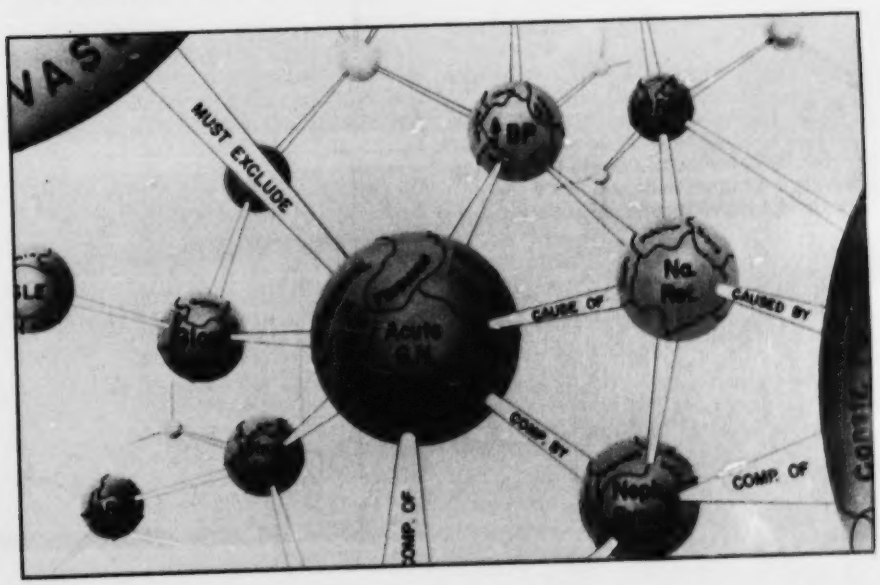
Future Program Directions

In the 1980's, program administrators believe, the network of biotechnology resources will continue to face escalating costs, obsolescence of equipment, and increasing national need for these resources. To offset the cost of supporting and developing the resources most needed by biomedical scientists, the program will encourage mature resources to become self-supporting via user fees or other funding sources. The program will continue to use workshops to determine the need for and uses of evolving technologies and to make these resources accessible to biomedical scientists. The program will also continue to support biomedical engineering resources, computer technology, and further development of instruments for the study of biological structure and function.

Instrumentation for the study of biological structure and function will include new, state-of-the-art liquid chromatography-mass spectrometry facilities to analyze biological materials present in the body; additional high-voltage electron microscopes for high-resolution studies of cell morphology and structure; more scanning transmission electron microscopes for localizing heavy atoms in biological specimens; and NMR and acoustic-imaging resources to complement roentgenography and light microscopy for visually scanning the internal structures of the body.

Biomedical engineering resources developed in the 1980's will include additional specialized microsensors for in vivo monitoring of chemical and physical events, and protective, bioinert materials to be used in microsensors and prosthetics. Support will continue for computer simulation and modeling resources to measure and image such physiological processes as circulatory mass transport, blooo-tissue exchanges, membrane exchange kinetics, and ionic membrane transport and for the engineering of graphic displays, which has accompanied the technology explosion in computer science.

Finally, the program's continued support of biomedical computing resources will include very large-scale integrated (VLSI) circuits, mini- and microcomputers, large-scale computer networks, application of artificial intelligence, and workshops to ensure the understanding and use of these resources.



Representation of a computerized knowledge base focused on kidney diseases. The Biotechnology Resources Program will continue to support the development and application of artificial intelligence to solve biomedical problems.

Animal Resources Program

Program Description

Biomedical researchers currently need animals for a variety of purposes. Nonhuman primates that closely model human physiological systems are particularly critical to studies of reproductive biology, neurophysiology, and behavior. Some species of animals are excellent models of human diseases such as diabetes or of human processes such as growth and metabolism. To meet the need for well-nourished, disease-free animals with known genetic backgrounds and the equal need to develop animal resource facilities, the Division of Research Resources established its Animal Resources Program (ARP) more than 15 years ago.

The ARP is comprised of two subprograms. The Primate Research Centers (PRC) Program supports seven regional primate research centers. The Laboratory Animal Sciences Program (LASP) supports specialized animal models and colonies, primate breeding, and a variety of other animal resource projects.

Regional Primate Research Centers

U.S. scientists have been concerned since the mid-1940's about the scarcity of nonhuman primates and research facilities and the lack of data on primates. To establish specialized facilities where biomedical scientists could study primates to learn about human health problems, the NIH initiated the PRC Program in 1960. Within 5 years, seven centers had been completed, forming the largest primate research base of its kind in the world. Serving as regional and national resources, the centers are located in Beaverton, Oregon; Seattle, Washington; Southborough, Massachusetts; Atlanta, Georgia; Madison, Wisconsin; Covington, Louisiana; and Davis, California.

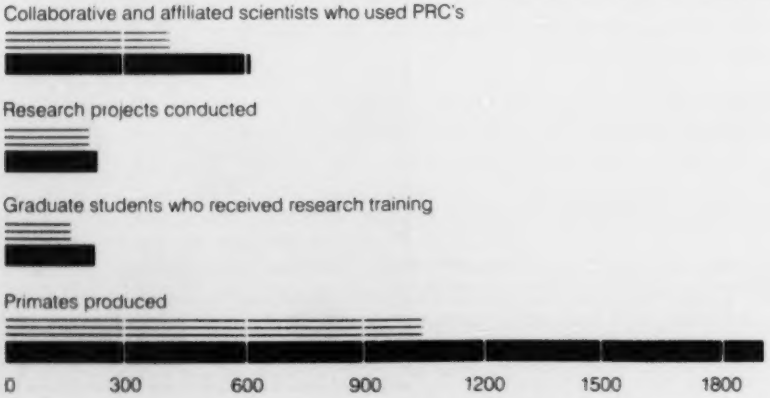
Each center has a primary research focus and is affiliated with a host academic institution. Primate center operations are supported by grants awarded by the DRR Animal Resources Program to the host institution or to foundations that serve as grantee institutions. Currently, these base grants support administrative, operational, and research costs, including salaries of the center staff.

Center research projects are funded by various NIH institutes, other Federal agencies, and private foundations through grants and contracts that are held by core staff and by collaborative or affiliated scientists. Through their use of nonhuman primate models, these scientists have contributed significantly to biomedical research. Significant advances, based upon findings in animal investigations, have been made in reproductive biology, infectious diseases, behavioral sciences, neurosciences, toxicology, nutritional and metabolic diseases, and environmental health.

Primate Breeding and Resources

The ARP supports primate breeding and resource projects to offset the decline in populations of wild primates from foreign countries, which have restricted exports. Recent conservation efforts and the classification of primate species by the Convention on International Trade in Endangered Species have made it nearly impossible to import

Productivity Indicators of the Primate Research Centers Program in FY 1980 Compared with FY 1975



Rhesus infant being weighed at a regional primate research center. The seven primate centers supported by the DRR Animal Resources Program form the largest primate research base in the world.

the rhesus monkey, long considered a standard laboratory primate. Other species needed for biomedical research are equally difficult to obtain.

Primate breeding projects are supported by either contracts or grants. Contracts provide for the production of animals for general distribution to NIH extramural investigators. The goal by the mid-1980's is to provide 1,200 rhesus monkeys, 150 cynomolgus monkeys, and 400 squirrel monkeys. Grant-supported primate breeding projects seek to establish nuclear production colonies of baboons, marmosets, and owl monkeys and to determine proper husbandry techniques for maintaining them.

Laboratory Animal Resources

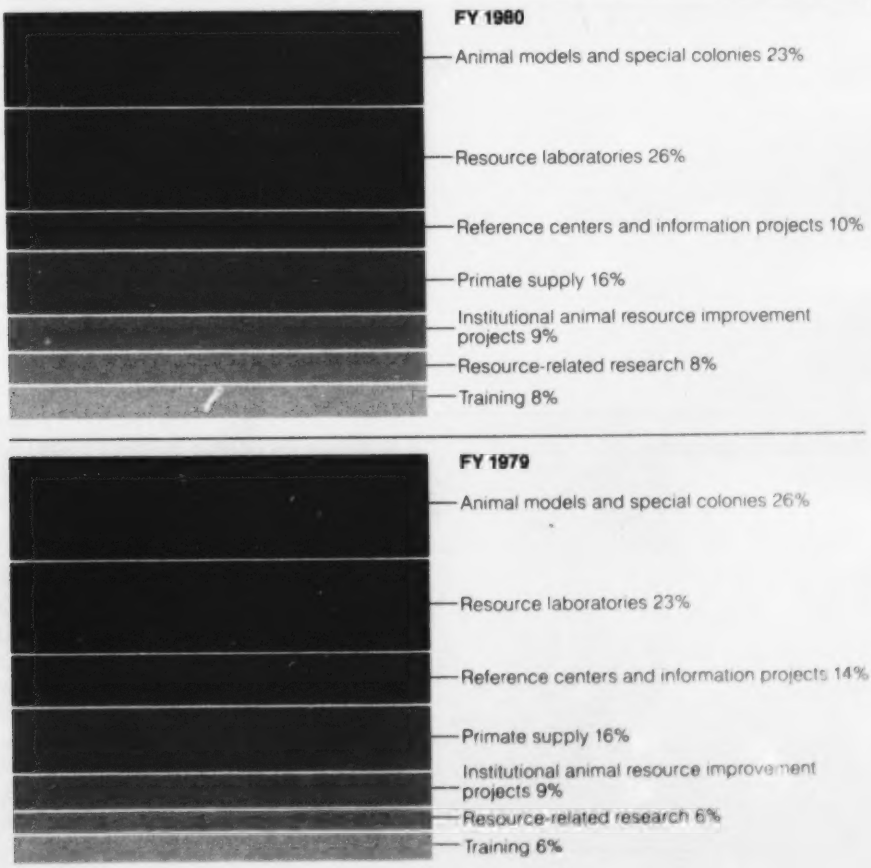
The Laboratory Animal Sciences Program, established by the ARP in the mid-1960's, supports nonprimate projects designed either to improve the quality of animals used in biomedical research or to enhance the availability of animals with special characteristics of interest to researchers.

Animal Models and Special Colonies. Many experiments to understand human growth, metabolism, and disease require genetically and environmentally controlled animal models. The objectives of animal model projects are: 1) to define, characterize, and exploit the relevant biological attributes of selected animals that display potential for use in biomedical research; and 2) to establish, improve, or expand special colonies of well-characterized animals of proven value for biomedical research that are not generally available from other sources.

Resource-Related Research. These projects are funded to investigate the etiology, pathogenesis, and control of naturally occurring animal diseases that can distort research data. Resource-related research projects have been accorded high priority by the Animal Resources Review Committee.

Institutional Animal Resource Improvements. The program supports improvement projects to help institutions upgrade their animal facilities and develop centralized programs of animal care in compliance with the Animal Welfare Act and DHHS policies on the care and treatment of animals. Funds are used for animal cages that meet current regulations, general sanitation equipment such as cage washers, renovation of animal facilities, and salaries of trained professional and technical personnel. Projects are supported for up to 3 years, after which the institution is expected to assume financial

Funded Project Areas Comprising the Total LASP Budget for FY 1979 and FY 1980



To understand human growth, metabolism, and disease, investigators sometimes require exotic animals such as the echidna, or spiny anteater. The DRR Animal Resources Program supports many animal models and colonies, particularly those with applicability to broad areas of research.

responsibility for its basic animal resource. From 1972 to 1980, 93 institutions received improvement grants totaling approximately $12.2 million.

Resource Laboratories. Resource laboratories have been a major program activity for over 10 years. Most resource laboratories are institutional, but some serve more than one institution in a metropolitan or regional area. The total number of 13 to 16 supported laboratories has remained relatively constant in recent years, although the institutions receiving awards have changed.

The objectives of these laboratories are: 1) to provide improved animal health programs through investigation of naturally occurring diseases and related laboratory animal problems; 2) to support studies resulting in new information on diseases of laboratory animals and their etiology; 3) to aid in discovering new laboratory animal models of human disease; and 4) to develop resources, including tissues, slides, and photographs, for research and training.

Reference Centers and Information Projects. Reference centers and information projects supported by the program include the Registry of Comparative Pathology, which provides consultation, publications, training, and research focused on comparative pathology; an Animal Model Reference Center with a sperm bank for animal models; and publication of the *Laboratory Primate Newsletter.*

Training. Training in laboratory animal science prepares individuals to provide professional care of laboratory animals, to manage central animal resources, and to aid investigators through expert knowledge of laboratory animal biology and research methods. Trainees are also prepared to participate in teaching graduate students and young investigators and to pursue their own research independently or in teams. Eight active training programs with a total of 29 trainee positions were funded in FY 1980. Since the inception of LASP grants and fellowships, 154 trainees and fellows have completed training; over 90 percent have stayed in the field of laboratory animal medicine.

Program Highlights

A recent survey pointed out that FY 1980 marked the beginning of a decade of challenges. The survey, which forms the foundation for the program's 5-year plan (1982–1986), was conducted for the program by the National Academy of Sciences' Institute of Laboratory Animal Resources (ILAR). It analyzed the current status of and future requirements in the United States for research animals, animal research personnel, facilities, and programs. The survey noted particularly the decreased number of animals used in research, possibly due to the shift from short-term to long-term animal studies; the increased cost of primates, due in part to reduced availability; the need for renovation or replacement of animal resource facilities and equipment; and the need for more veterinarians trained in laboratory animal medicine to provide quality animal care. The 5-year plan, published this year, responds to these changes and needs.

During FY 1980 the program continued to support primate breeding, the research capability of the primate research centers, improved laboratory animal care, further development of animal models of human disease, renovation of animal research facilities, and training of laboratory animal specialists. The specific activities of each program area are detailed in the following paragraphs.

PRC support in FY 1980 enabled 138 center staff scientists and 615 affiliated, collaborative, and visiting scientists to conduct research at the primate centers.

Because the complex web of primate fertility is so similar to the human system, primates are ideal models for studying human reproductive problems.

Primate Research Centers

During FY 1980 the primate centers extended their resources and services to a larger user group, stepped up training efforts, increased primate breeding for center use, and maintained center scientific productivity.

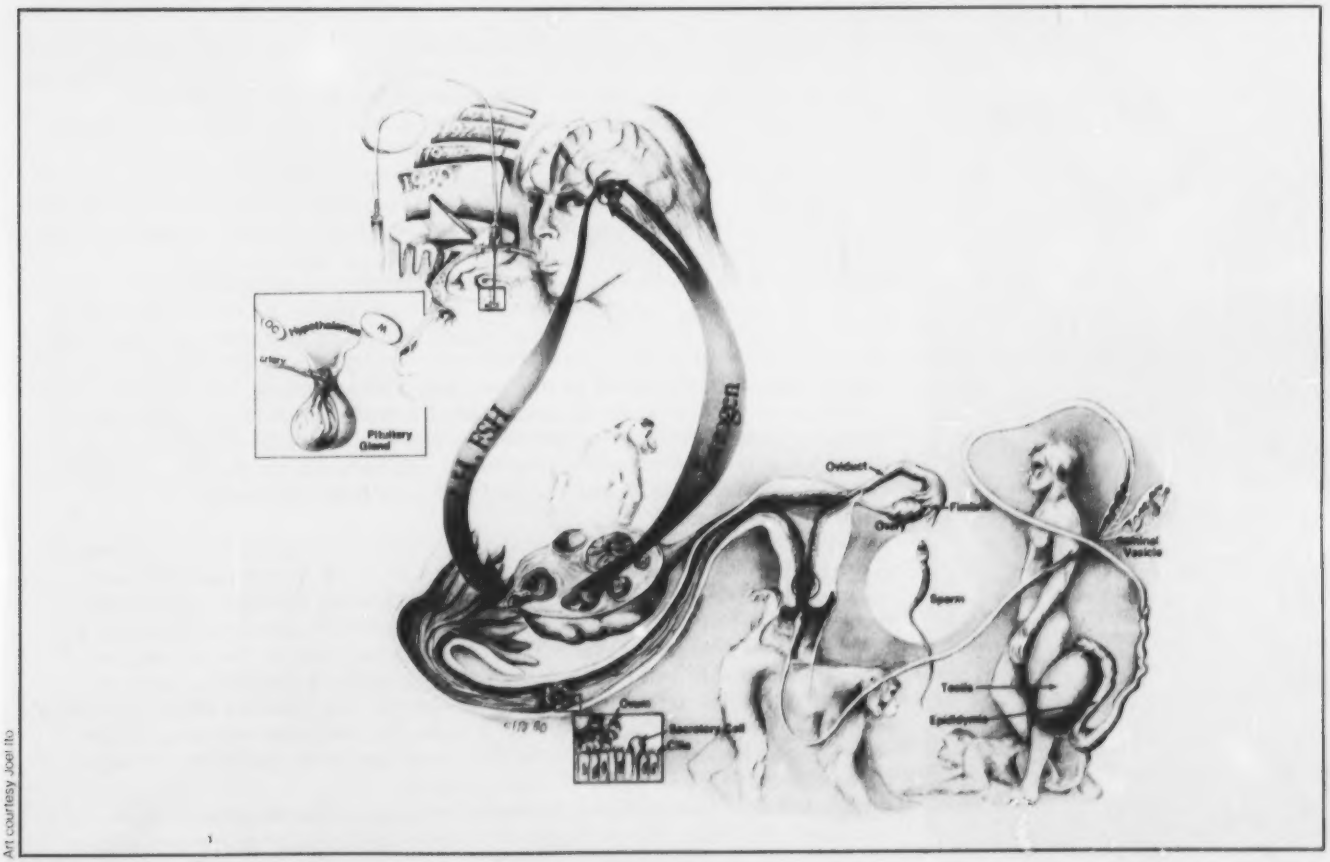
Core support of $16.131 million enabled 138 core staff scientists to conduct research at the centers. The program also provided salary support for 654 doctoral level, technical, and administrative staff members. Center resources and services were made available to 615 affiliated, collaborative, and visiting scientists from various academic institutions, and 232 graduate students engaged in thesis-related research in these unique training environments. Finally, the centers provided over 7,000 biological specimens to 292 scientists at various U.S. research institutions.

A significant and costly problem confronting the centers during the fiscal year was the continuing restriction on export of certain feral nonhuman primate species from their countries of origin. To compensate, the centers' domestic breeding programs produced approximately 1,900 primate infants and fetuses, representing approximately 70 percent of their total primate requirements. The other 30 percent were purchased or acquired by exchange. Small nuclear colonies of less commonly used primate species were also maintained to assure their survival for potential future research needs. In all, approximately 12,000 primates (45 species and subspecies) were maintained by the centers.

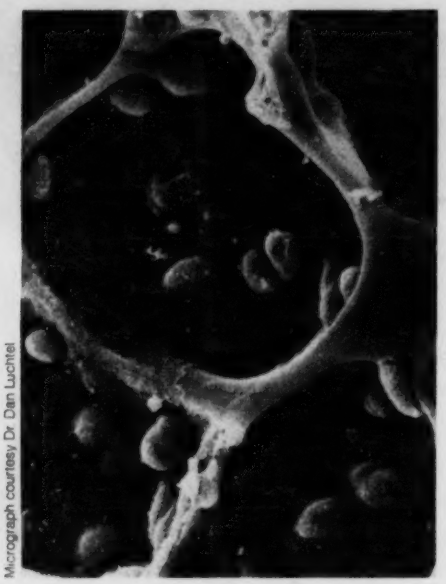
Scientific productivity at the centers remained strong, with over 600 journal articles and books published by the core staff and affiliated and collaborative scientists in FY 1980. Center research accomplishments spanned a broad range of areas from neurophysiology and reproductive biology to cardiovascular and environmentally induced diseases. Following are some highlights of this research.

Reproductive Biology

Exploring the Basic Biology of Reproduction. Investigations of primate fertility by four scientific teams at one center may eventually lead to treatment of endocrine diseases of the reproductive system or to relief of menopausal symptoms without causing side effects. Taking advantage of the similarity of the primate and human reproductive systems, the researchers are studying reproduction from the brain to the ovaries, fallopian tubes, and testes and learning how the brain, pituitary, and gonads function in



Art courtesy Joel Ito



Micrograph courtesy Dr. Dan Luchtel

A primate model is being developed by PRC researchers, which may lead to preventive treatment of respiratory distress syndrome (RDS). RDS is often fatal in premature infants whose lung alveoli collapse to make breathing almost impossible. Above, magnified 2,600 times, are the alveoli of a healthy premature monkey.

Rhesus sperm. Investigations of primate fertility by four scientific teams at one primate center this year may eventually lead to treatment of endocrine diseases of the reproductive system.

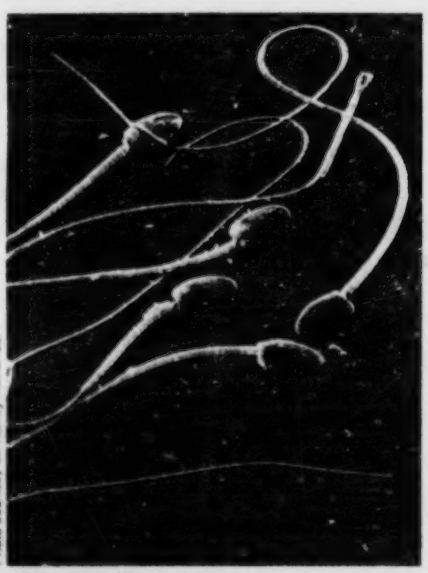


Photo courtesy Dr. Nancy Alexander

unison to maintain the reproductive hormonal rhythms. Some evidence points to the possibility of a pelvic clock; that is, the possibility that the ovaries may control their own cycle by secreting hormones that influence the brain.

Effect of Oral Contraceptives During Early Pregnancy. Researchers at one primate center studied the effects of oral contraceptive use during early pregnancy. They found that administration of an oral contraceptive during early pregnancy caused an increased level of early fetal death, but not a higher incidence of birth defects as had been previously suggested. Center researchers administered an oral contraceptive to rhesus monkeys at 2, 4, and 10 times the recommended human dosage. Sixty-three percent of the treated pregnancies produced offspring with no indications of birth defects. However, 37.7 percent resulted in abortion or stillbirth, showing a significant increase over the spontaneous rate of fetal death in untreated pregnancies.

In Vitro Fertilization of Primates. A center research team has begun developing a primate model to study in vitro fertilization and implantation, the process that resulted in the world's first human "test-tube baby." This primate model is expected to generate data, scanty at present, on environmental changes and consequent chromosomal abnormalities in fetuses. The model will also enable researchers to isolate phenomena in the uterine environment and to measure their effects more precisely. They will establish the hormonal patterns of estrogens, progesterone, and pituitary gonadotropins in the squirrel monkey during its unmated cycle, mating cycle, and pregnancy. Armed with these data, they will then fertilize ova from squirrel monkeys and chimpanzees in vitro. They plan to develop in both species a method for successful implantation and pregnancy, which may eventually be used to alleviate current implantation and pregnancy problems in humans.

Neurophysiology, Developmental Behavior, and Communication Disorders

Brain Insulin and Obesity. Most people and laboratory animals tend to maintain a remarkably stable weight, even if given unlimited access to food. Whether they are obese or thin, people's established weight appears resistant to change. Metabolic studies of baboons were done at one center to determine whether a regulatory system for satiety exists. These studies indicated that insulin in cerebrospinal fluid (CSF) may regulate body fat by carrying a message from the body to the brain. When researchers infused insulin into the baboons' CSF, the baboons began to eat less. According to the center scientists, the increased CSF insulin may be interpreted by the brain to indicate increased fat stores, and the brain responds by reducing meal size and by decreasing insulin levels.

Early Determinants of Coping Behavior Identified. According to long-term research at one primate center, patterns of coping behavior in nonhuman primates may be determined as early as the first few months of life. Several experiments with group-caged and individually caged infants suggested that primates which do not experience adequate stimulation or socialization early in life are less able to cope with weaning and later psychosocial stresses. The animal's early experience tends to favor one of two different types of stress-response patterns: adequate early stimulation favors the adrenomedullar-sympathetic (flight-fight) response; inadequate early stimulation favors development of the pituitary-adrenocortical (conservation-withdrawal) response.

Primate Model Developed for Teaching Communication Skills to Handicapped. Researchers at one primate center have demonstrated that the symbol system used to teach chimpanzees language is also successful in teaching basic communication skills to mentally retarded children. The chimpanzees were shown to be able to use computer keyboard symbols referentially, symbolically, and communicatively. They learned to push buttons for appropriate words to request tools of one another, contingent upon tasks to be solved. Several mentally retarded children improved their understanding and use of language using the symbol system. Further development of electronic and computer systems to facilitate language acquisition is being pursued at the center.

Cardiovascular Diseases

Dietary Lecithin Lowers Blood Cholesterol. Recent experiments with rhesus monkeys at two primate centers demonstrated that dietary lecithin lowers blood cholesterol and triglycerides. A 10-year, lecithin-supplemented diet lowered cholesterol in a group of monkeys by 23 percent and decreased the level of plasma triglycerides 34 percent by enhancing their removal from the blood. Lecithin also lowered low-density lipoprotein (LDL) cholesterol but tended to increase high-density lipoprotein (HDL) cholesterol. Elevated LDL levels correlate statistically with coronary heart disease, while high levels of HDL are negatively associated with heart disease. The results are promising, but the investigators believe more research must be completed before lecithin becomes an acceptable part of any cholesterol-lowering regimen.

Primate Model of Atherosclerosis Developed. Atherosclerosis, the formation of cholesterol-laden plaque in the arteries, is a major health problem in the United States.

Recent primate center studies with rhesus monkeys demonstrated that dietary lecithin lowers blood cholesterol and triglycerides.

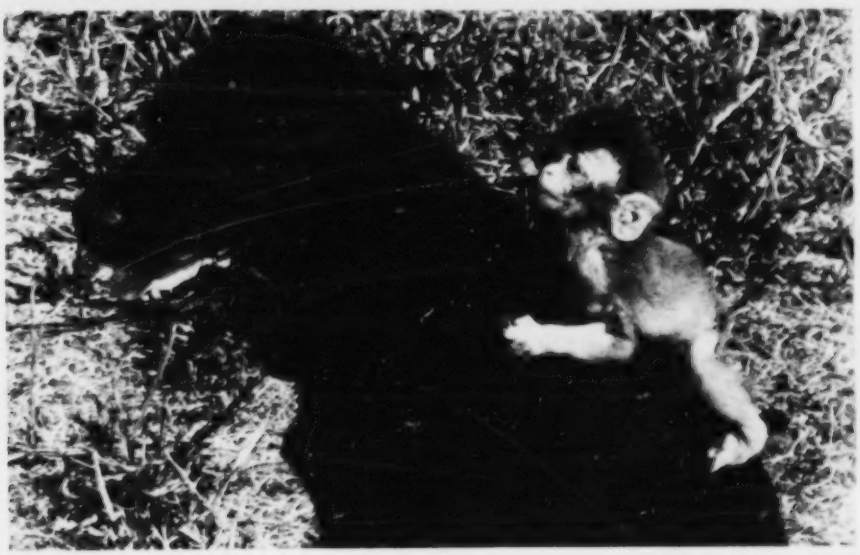
Study of a primate model is beginning to elucidate the many aspects of this complex problem. Some center research indicates that damage to the endothelial lining in the arteries can create atherosclerosis. Other research suggests that reduction of 100 mg/dl in plasma cholesterol concentration results in reduction in plaque size of 0.5 percent per month. Primate experiments also confirm the relationship of stress to increased atherosclerosis, indicating that aggressive, "type A" personalities are more prone to atherosclerosis than more easygoing, less stressful types.

Primate Breeding and Resources

In FY 1980 the Animal Resources Program funded five grants and six contracts for the domestic breeding of nonhuman primates, a Caribbean Primate Center, and a Primate Supply Information Clearinghouse.

The 11 primate breeding projects supported by the program were quite productive. By July 1980, 1,653 female rhesus, 150 cynomolgus, and 138 squirrel monkeys were in production colonies. Colony births during FY 1980 included 1,198 rhesus, 91 cynomolgus, and 22 squirrel monkeys. All females were kept for colony expansion. However, 250 male rhesus monkeys were provided for a polio vaccine testing program; 250 rhesus monkeys were supplied to NIH grantees; and 113 young and adult cynomolgus and 5 squirrel monkeys were supplied to investigators. Because of the general difficulties in maintaining optimum squirrel monkey production in captive colonies, a grant was funded to study the reproductive problems of this species.

The Primate Supply Information Clearinghouse facilitates conservation and maximum research use of available primates by matching investigators' requests for primates,



Rhesus infant on the back of its surrogate mother. Long-term research at one primate center has identified early stimulation and socialization experience as important determinants of later ability to cope with psychosocial stresses.

primate tissues, and related resources with breeding colonies that have these items available. In FY 1980 it placed 2,783 primates, published 51 formal requests for cadavers, tissues, and other specimens in its weekly bulletin, and handled many more requests by phone.

The Caribbean Primate Center is a valuable resource for research on primate social behavior and tropical diseases. It includes a basic primate colony on the Puerto Rico mainland and semifree-ranging primate colonies on an island off the coast of Puerto Rico. This year it tested Dengue type 1/S-1 vaccine and tetanus vaccine in rhesus monkeys and continued to be an important breeding center for the National Institute of Neurological and Communicative Disorders and Stroke.

Laboratory Animal Resources

During FY 1980 the program succeeded in developing useful animal models and colonies, improving the health of laboratory animals, upgrading animal research facilities, and expanding training opportunities. The program awarded funds totaling $7.119 million to support 64 animal research and resource projects, eight institutional training programs, and one individual fellowship.

Animal Models and Special Colonies. Support for projects related to animal model and colony development decreased slightly from FY 1979's budget. A total of 24 projects received support, including one new resource grant and five ongoing contracts. Three animal model projects were funded to identify, characterize, and make available new animal models of human genetic diseases. Some of these projects resulted in well-

established models that now have separate grant support, including a horse model of combined immunodeficiency disorders and a dog model of diabetes mellitus. Models still in the early stages of development include cat models for mucolipidosis and inherited tremors and a dog model for inherited hyperreninism.

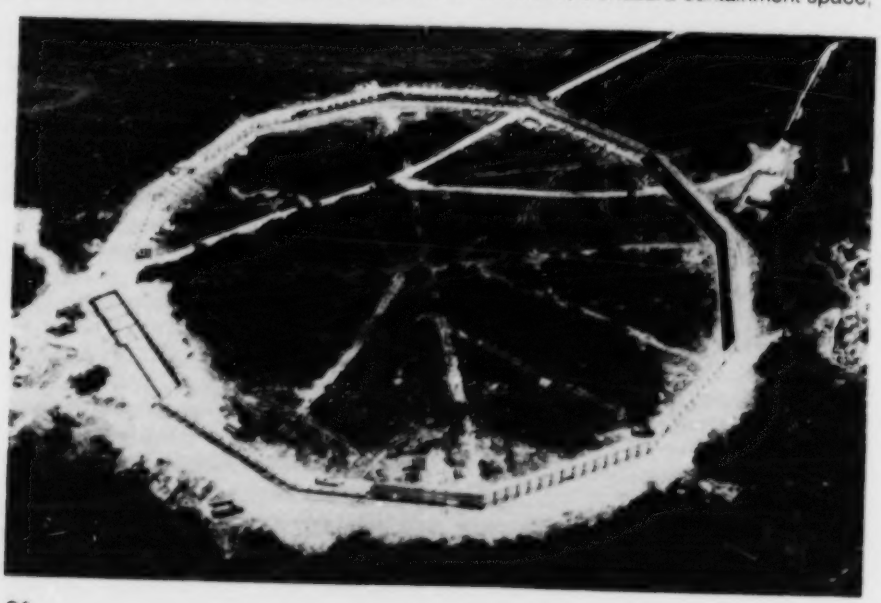
Several marine invertebrate projects continued to study the problems of mariculture and laboratory maintenance of certain species of sea hares, sea urchins, and squids. In the past, declining natural populations and maintenance problems limited the number of these animals available for research. In the future, laboratory breeding may lead to a continuous supply of these marine invertebrates, which are particularly important to neurological research.

Supported colony projects included colonies of hamsters, congenic mice, a rabbit inbred and mutant stock resource, and a mouse mutant gene resource. The mouse resource, a typical colony project, was established with an original population of 140 mutants. It focuses on endocrine, neurological, and immunological problems. The resource maintains these mutant stocks and provides them to other laboratories for either breeding stock or experimental use. This year it added new mutants to the colony for initial characterization and linkage testing. One mutation, in which chromosomally male individuals develop as females, is believed to be the first Y chromosome mutation found in mammals. Study of this Y^h mutation will further understanding of the role the Y chromosome plays in sexual differentiation.

Resource-Related Research. Although the number of resource-related projects has remained at around 9 to 11 in recent years, recognition of the adverse impact of laboratory animal diseases and environmental factors on research continues to grow. As a result, two new projects to study laboratory animal disease problems were funded in FY 1980: a study of experimentally induced mucoid enteritis in rabbits and a study of the pathogenesis of parvovirus infection in canines. Other FY 1980 projects made progress toward the diagnosis and control of mammalian encephalitozoonosis, canine brucellosis, and respiratory mycoplasmosis in rodents. The encephalitozoonosis project resulted in development of a simple, rapid test for detection of serum antibodies in rabbits. Reported infection rates of rabbit populations ranging from 20 to 90 percent demonstrate the importance of this test in alleviating a situation that could distort and invalidate research data.

Other projects included a census of rhesus monkeys in northern India and a study of significant features of the natural habitat of West African rain forest primates. Information from the Indian project continues to guide the conservation and management of rhesus monkeys and will be important in evaluating the potential future supply of rhesus monkeys for biomedical research.

Institutional Animal Resource Improvements. Institutional improvement projects have been supported since the inception of LASP. Over the past 8 years, 93 institutions have received improvement grants through awards totaling approximately $12.2 million. Although inflation and the need to fund new projects has lessened the amount available for improvement projects in the past few years, the program funded four new grants this year for equipment renovation, replacement, or additions, biohazard containment space,



This 6-acre baboon corral in San Antonio, Texas, holds the largest baboon breeding colony in the United States. It represents stepped up domestic breeding efforts supported by the DRR Animal Resources Program.

Researchers at one animal resource laboratory have developed methods to control the lungworm disease transmitted by ingestion of F. hirthi larvae (above), which afflicts many beagle dogs used for research. ARP support contributed to prevention of laboratory animal disease and improvement of laboratory animal care this year. Laboratory animal health will continue to be a program priority in the 1980's.

and other facility improvements. The great need for renovation of facilities and for repair and replacement of laboratory equipment was noted in the ILAR survey.

Resource Laboratories. Sixteen laboratories were funded in FY 1980, comprising approximately 28 percent of the LASP budget. Laboratory activities ranged from surveillance and monitoring to research on important laboratory animal disease problems. A team of clinicians, virologists, and pathologists at one laboratory confirmed the presence of LCM virus in mice and alerted other investigators at the laboratory who were puzzled by unexplained variances from anticipated results when using certain tumor cell lines. The LCM virus was ultimately isolated from five laboratories and 15 tumor lines. The timely recognition and control of this problem eliminated the risk of human exposure and prevented the publication of data compromised by this latent viral infection.

Another resource laboratory was consulted when mouse pox, a serious disease, struck 30,000 mice at a medical center. The laboratory reviewed decontamination and vaccination procedures and formulated recommendations for general management and renovation of the facilities. The prompt diagnosis and control measures saved over two-thirds of the animals and prevented transmission of the disease to other animal facilities.

Reference Centers and Information Projects. This year the Registry of Comparative Pathology augmented its collection with 1,600 specimens from primates and other laboratory animals, domestic and wild animals, fish, and birds. These materials were distributed to users for exhibits and lantern and microscopic slide sets and were used as the basis for a number of publications. The registry responded to requests for consultation, published the *Comparative Pathology Bulletin* quarterly, and prepared for sale a handbook entitled *Animal Models of Human Disease*. It also held a workshop on needs for new animal models and offered a course in comparative pathology.

The Immunohematological Reference Center continued to produce, standardize, and unify available resources that identify red blood cell groups, histocompatibility antigens, and other immunogenetic markers in the dog. This year it focused on production of reagents for histocompatibility antigens. During the last reporting period, a total of 264 animals were typed for erythrocyte antigens, 279 animals were characterized for histocompatibility antigens, and 382 ml of various typing sera were provided to qualified investigators.

Training. The ARP in FY 1980 maintained eight active training programs with 29 trainee positions. In addition to these institutional programs, one individual postdoctoral fellowship was active at the end of the fiscal year. For the past 5 years, institutions with active training programs and diagnostic resources have been encouraged to employ veterinary students during summers. Seven institutions and 13 students participated in summer programs during the past year.

Future Program Directions

In the 1980's the Animal Resources Program will face the continued scarcity and high cost of primates. The demand for trained laboratory animal specialists may continue to exceed the supply, and institutions will need renovations to meet federal animal welfare standards. To meet these needs, the program plans to implement its 5-year plan. However, the planned actions summarized below are contingent upon what funds will be available.

Primate breeding will be stepped up to assure a stable supply of essential primates for NIH extramural research, and the primate research centers plan to reach near self-sufficiency in primate supplies for the centers by the mid-1980's. To improve center scientific productivity, the centers will work toward closer center-host-institution relationships, retaining experienced staff, and improving physical plant and equipment.

The Laboratory Animal Sciences Program in the eighties will give priority to projects investigating the effects of laboratory animal disease on research results. It will continue to support development of animal models and colonies, particularly those applicable to a broad user group. Finally, training programs will be expanded to combat the continued shortage of veterinarians with specialized training in laboratory animal science.

Minority Biomedical Support Program

Program Description

Today, minority students and faculty have greater opportunities to conduct research in well-equipped scientific settings because of support by DRR's Minority Biomedical Support (MBS) Program. Previously, the limited involvement of minority institutions in biomedical research discouraged minority students from entering the field and placed those who did at a competitive disadvantage when they applied for advanced training. Moreover, faculty members at minority institutions were frequently unable to engage in research because of heavy teaching loads and lack of necessary facilities and equipment.

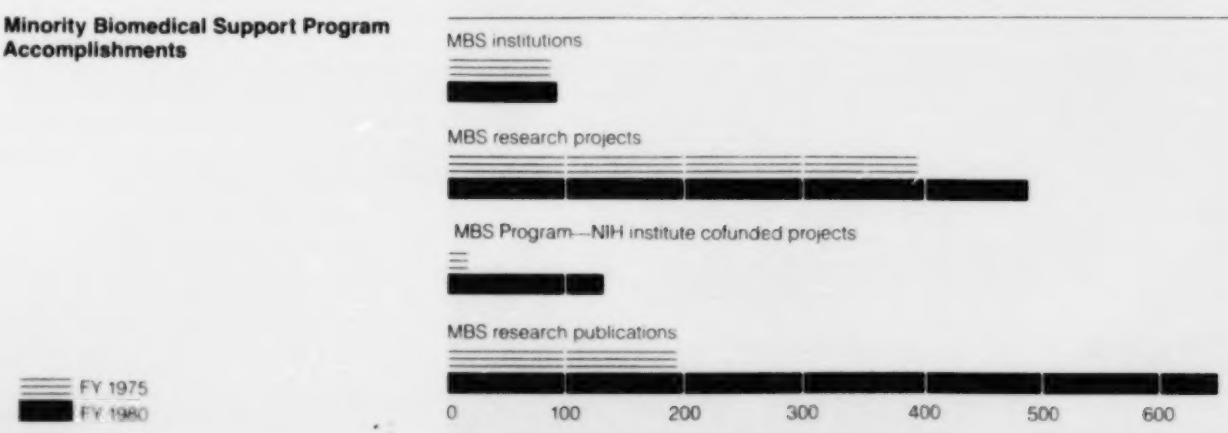
To correct the underrepresentation of minorities in biomedical research and to eliminate obstacles to their participation, the DRR Minority Biomedical Support Program was begun in 1972. The major thrust of the program is through grants to develop minority student, faculty, and institutional involvement in biomedical research. Funds are provided for scientific equipment, facility renovations, improvement of animal care facilities, support of students, travel to professional meetings, and release of faculty from teaching to conduct biomedical research. A unique feature of the program is its emphasis on undergraduate participation in all aspects of biomedical research.

Through its cooperative agreements with nearly all 11 institutes of the NIH and the National Institute of Mental Health, the program is the cornerstone of the NIH's extramural affirmative action program. The purpose of these intra-agency agreements is to provide MBS investigators with the opportunity to participate in areas of research sponsored by various institutes of the NIH. The MBS Program staff identifies MBS research projects that appear to fit each institute's mission. If the institute approves the project and has funds available to support it, it shifts funds to the MBS Program, which then acts as a clearinghouse and managing unit. By becoming acquainted with the institute's research focus and grant application requirements, MBS institutions and investigators can soon compete equally for institute grants through the normal application procedure. In this way, the intra-agency agreements augment MBS Program efforts to help ethnic minority scientists and educational institutions enter the mainstream of the nation's biomedical research effort. In FY 1980, 129 MBS projects were supported through intra-agency agreements—a tremendous increase since 1975, when intra-agency agreements supported only 8 projects.

Program Highlights

Fiscal year 1980 marked continued support for the research capability of MBS institutions and continued entry of minority scientists and students into biomedical research. An increased MBS appropriation to $18.089 million was used to fund 79 institutions.

Minority Biomedical Support Program Accomplishments



including 8 new grants, and positions for 1,030 undergraduates, 370 graduate students, and 660 faculty.

Institutional Development. To develop the research capabilities of grantee institutions and to enhance their research productivity and ability to compete for regular research grants, the program funded state-of-the-art research equipment, instruments, and resources at appropriate institutions; sponsored four grantsmanship workshops; and established an agreement with the DRR Biotechnology Resources Program to extend PROPHET, a computerized network for processing biomedical research data, to several MBS institutions.

Three years of MBS support enabled one institution to sufficiently develop its cellular and molecular biology resources to the point that it is now competitive for regular research grants. Similarly, a consortium of five MBS institutions without biomedical research capabilities and with no access to centrally shared research resources used MBS funds this year to establish a complete electron microscopy resource and a high-resolution spectrometry resource, which can be linked by computer to the PROPHET system. MBS support also culminated in the establishment of a productive immunology laboratory, whose principal investigator, having published 21 papers on immunology in the past 3 years, is now considered an authority on immunological research and a pioneer in immunodiagnosis.

During FY 1980 the MBS Program supported 79 institutions and positions for 1,030 undergraduates, 370 graduate students, and 660 faculty

The four grantsmanship workshops planned and sponsored by the program were attended by 310 faculty members of MBS institutions. The objective was to strengthen faculty ability to write high-quality research grant proposals that would be competitive in the peer review process. The workshops included illustrated lectures on common problems and deficiencies in research grant applications, development of a typical research grant budget, the NIH peer review process, and an overview of NIH grant programs.

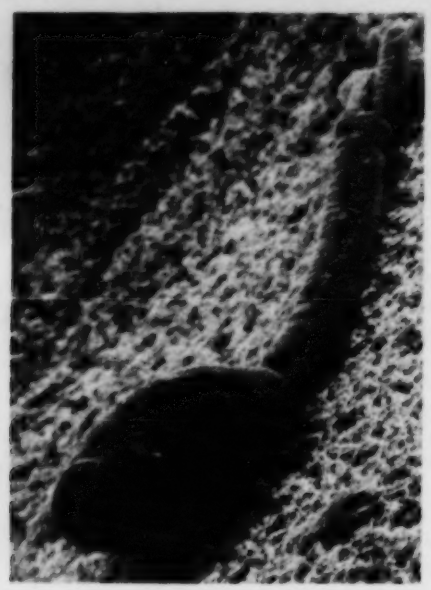
In collaboration with Biotechnology Resources Program administrators, MBS Program administrators provided MBS grantees with the opportunity to propose their institutions as PROPHET user sites. The Biotechnology Resources Program demonstrated the PROPHET system at the MBS program directors meeting in December 1979 and during the annual MBS symposium. As a result, four MBS institutions submitted proposals for consideration as PROPHET user sites. The proposals have been approved and funded for FY 1981. Another collaborative effort was initiated when the General Clinical Research Centers Program offered to assist one medical school in preparing an MBS grant application to develop its clinical research capability. If the application is approved and cofunded by the MBS and GCRC Programs, it will assist the institution in developing the capacity to compete later for a general clinical research center grant.

Faculty and Student Development. MBS research productivity was further enhanced by faculty and student participation in the program and in biomedical research. The annual reports received from 44 grantees noted that 302 MBS undergraduates received B.S. degrees. Of these, 62 were admitted to medical school, 27 were admitted to dental school, 80 entered graduate school, and 57 went on to health-related careers. All graduates from MBS-supported junior colleges transferred to 4-year colleges. MBS undergraduates produced 300 papers presented at scientific meetings. Most of the estimated 100 MBS graduate students who completed master's degrees this fiscal year are continuing doctoral training. Although only 10 MBS institutions have Ph.D. programs, 10 to 15 graduate students received Ph.D.'s in FY 1980. This brings to 50 the total number of Ph.D.'s awarded since inception of the program.

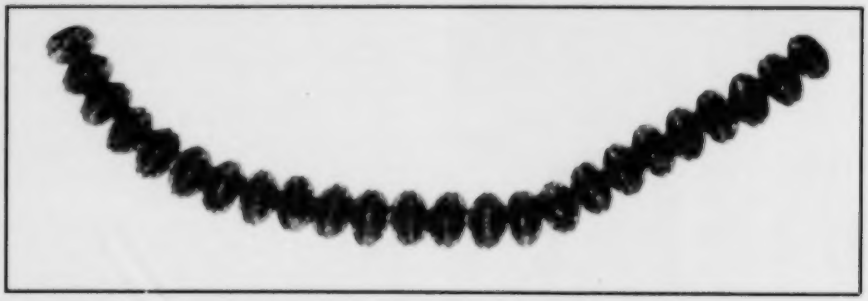
MBS faculty research productivity has steadily increased with 81 percent of the faculty publishing their research in 1978 compared to 53 percent who published in 1976 and 15 percent in 1974.

Faculty research productivity has steadily increased with 81 percent of the faculty publishing their research in 1978 compared to 53 percent who published in 1976 and 15 percent in 1974. Data for 1980, not yet complete, indicate a continuation of the trend. In addition, 82 percent of MBS faculty made research presentations in 1978 compared to 29 percent in 1974. In FY 1980 a number of faculty investigators won NIH grants through the national competitive application process, and several were appointed to NIH scientific review committees or advisory groups. At present, 30 past or present MBS faculty participants are members of NIH study sections, advisory committees, and councils. This is double the level of minority involvement just 2 years ago.

Research Accomplishments. Highlighting MBS faculty and student research last year was the eighth annual MBS symposium held in Atlanta, Georgia, in April 1980. Two Nobel laureates and several other well-known scientists, who were invited to present papers, joined the 1,400 MBS participants. Approximately 230 MBS research papers and 251 research project posters were presented. Several workshops on computer use and new research techniques were held, and more than 50 graduate and health professional schools had information booths. Following are several MBS research projects presented at the symposium or published in journals during FY 1980.



Researchers at one MBS institution continued development of a vaccine that may protect against schistosomiasis which affects more than 200 million people in the world and is caused by the schistosome parasite (above).



A chain of asexual algae cells cultivated as part of research on marine algae toxins at one MBS institution. The MBS research team has improved techniques for harvesting and purifying algae toxins, which may have potential use in developing drugs to fight disease (above right).

Potential Vaccine Against Schistosomiasis. Researchers at one grantee institution in Puerto Rico continued development of a vaccine against the tropical disease schistosomiasis. Caused by a parasite, this devastating disease affects 10 to 15 percent of Puerto Ricans and more than 200 million people in the world. Testing of the vaccine in laboratory mice has already demonstrated a significant level of immune protection.

Role of Hormones in Breast Tumor Growth. MBS-supported research on breast tumor growth this year has begun to delineate the role of hormones and certain hormone inhibitors on the rate of tumor growth. Investigators recently demonstrated that the compound CI-628, a female hormone antagonist that binds competitively to hormone receptors, induces tumor regression and terminates the synthesis of an important catalyst in tumor cells. They also showed that another female hormone antagonist, progesterone, results in blockage of the biological processes involved in tumor development. Since 40 percent of breast cancer among American women appears to be hormone-dependent, this work has important implications for treatment.

Marine Mollusk Model for Opiate Receptor Functioning. An MBS researcher collaborated this year with researchers at a non-MBS institution to investigate the marine mollusk *Mytilus edulis* as a model system for opiate receptor functioning in humans. The mollusk is a useful model for several reasons. Its neurons are larger than those in mammalian brain tissue and permit easy visualization of neuronal substructure. More than one microelectrode can be inserted into a single cell, providing exact intracellular recording of ionic changes that accompany opiate receptor binding. Finally, the invertebrate nervous system is considerably less complicated than the mammalian system and can be precisely monitored to detect the cellular and electrical effects of specific exogenous chemicals.

Improved Methods for RNA Fingerprinting. MBS researchers developed improved methods for in vitro radioactive labeling for RNA fingerprinting this year. A rapid iodination procedure involving the inactivation of phosphatase and RNase T_1 obtains a sample for high molecular weight RNA fingerprinting. When combined with two-dimensional gel electrophoresis, this procedure simplifies fingerprinting with iodinated RNA without interference from impurities. The procedure substantially reduces the time needed to conduct these key procedures in RNA fingerprinting research.

Harvesting and Purifying Marine Algae Toxins. MBS investigators at an MBS institution in a coastal area have been involved in toxicology and pharmacology investigations of marine algae. With growth and culturing facilities on the shore and ready access to algae and sea water with a range of salinity, the researchers are uniquely situated to study this problem. By varying the growth medium and environmental conditions of marine algae, these investigators have cultivated large volumes of cells under conditions that promote high toxin production, which laboratories more remote from abundant resource material have not been able to produce. The MBS team has also improved techniques for harvesting and purifying the toxic material. Major research laboratories have expressed interest in this development and have requested the algae toxin for use in their own research programs. Moreover, these toxins have potential use for developing drugs to treat disease, or for development of an effective treatment for human or animal intoxication from ingestion of toxic marine organisms or from their venoms.

Future Program Directions

Based on the 5-year plan (1982-1986) completed in FY 1980, the program will give priority to minority faculty and institutional development in the 1980's, but will continue to provide opportunities for student participation in research projects. Specific program goals are to continue providing guidance to MBS grantee institutions in grant application procedures and grant management; to develop and provide additional mechanisms for student exposure to research and for advanced research study; and to initiate administrative and management changes to improve program evaluation.

Biomedical Research Support Program

Program Description

The DRR Biomedical Research Support Program administers two institutional research grant programs, the Biomedical Research Support Grant (BRSG) Program and the Biomedical Research Development Grant (BRDG) Program.

The BRDG Program was established in 1977 to provide grants on a competitive basis to new, small, or developing institutions to expand and strengthen their health-related research. Since that time, many institutions have benefited from the program. Recently, however, the need for this program has diminished. Fewer applications have been received each year, with the majority coming from previously unsuccessful applicants. Therefore, the BRDG Program is no longer offered, and current grantees will be phased out by 1983.

The BRSG Program provides funds to institutions actively engaged in biomedical and behavioral research for short-term, emergency, low-cost, interim, and shared research resource needs not covered by other PHS research grants, or that can be provided most effectively or efficiently by BRSG funds.

When an investigator needs to learn a new skill or technique, when a promising project is in danger of interruption between grants or when a new idea requires pilot research, when essential equipment breaks down or when new equipment is necessary to continue research, these needs of investigators often are not specified for funding by other PHS grants or cannot be met in time by those grant mechanisms. To fill these gaps, the BRSG Program (formerly the General Research Support Grant Program) was authorized in 1960.

BRSG funds are intended to complement or supplement other types of PHS research grants. Unlike NIH research project grants, BRSG grants are designed for flexible use at the discretion of the grantee institution. One institution may use BRSG funds chiefly for shared equipment; another may use them to support new investigators or pilot research.

An investigator with a new or unexpected research cost not adequately met by a project grant can submit a request for BRSG funds to the BRSG program director at that institution. Advice on the merits of each request is provided to the program director by appropriate scientific and administrative staff. The program director then selects for funding those projects and centrally shared resources that most improve biomedical research at the institution.

The BRSG Program enhances the quality, increases the productivity, and reduces the cost of biomedical research at the nation's research organizations, health professional schools, academic institutions, and research hospitals. Funding of pilot studies to test the validity of new ideas and the feasibility of research methods encourages innovation and reduces the risk of major cost commitments to projects that might be unproductive. BRSG funds for new investigators, including minorities and women, enable them to set up laboratories, conduct initial research, and gain post-training research experience. Supporting a promising investigator to begin research immediately after completing training ensures that research momentum from the training period is continued and that research knowledge and skills are sustained.

FY 1980 Biomedical Research Support Grants by Type of Institution

Type of Institution	No. of Grants	Amount
Schools of medicine	117	$16,575,117
Other health professional schools	80	4,438,373
Other academic institutions	161	13,331,629
Hospitals	61	4,576,167
Health departments	2	160,072
Research organizations	85	5,584,193
	506	$44,665,551

BRSG funding of emergency and interim needs saves research projects from being interrupted or abandoned before completion. Occasionally, a research project requires redirection, the collaboration of other investigators, or the training of an investigator in a new or unfamiliar technique. Funding also becomes critical during temporary interruption of PHS project grant support, which can force professional and technical personnel into other activities, making them unavailable when project funding resumes. BRSG funding at this point keeps the staff on the project and prevents the need for costly reassembly and training of a new research team when project grant support is resumed.

BRSG funds are also used to support shared equipment not appropriately funded by other sources. When several investigators at one institution need the same instrument for their individual projects, but the high cost and intermittent use of the instrument for a single project may not justify its purchase, sharing of equipment minimizes research costs for each project by avoiding equipment duplication. Further, the availability of state-of-the-art equipment often reduces the time required to complete projects. This equipment may also improve the precision and reliability of findings.

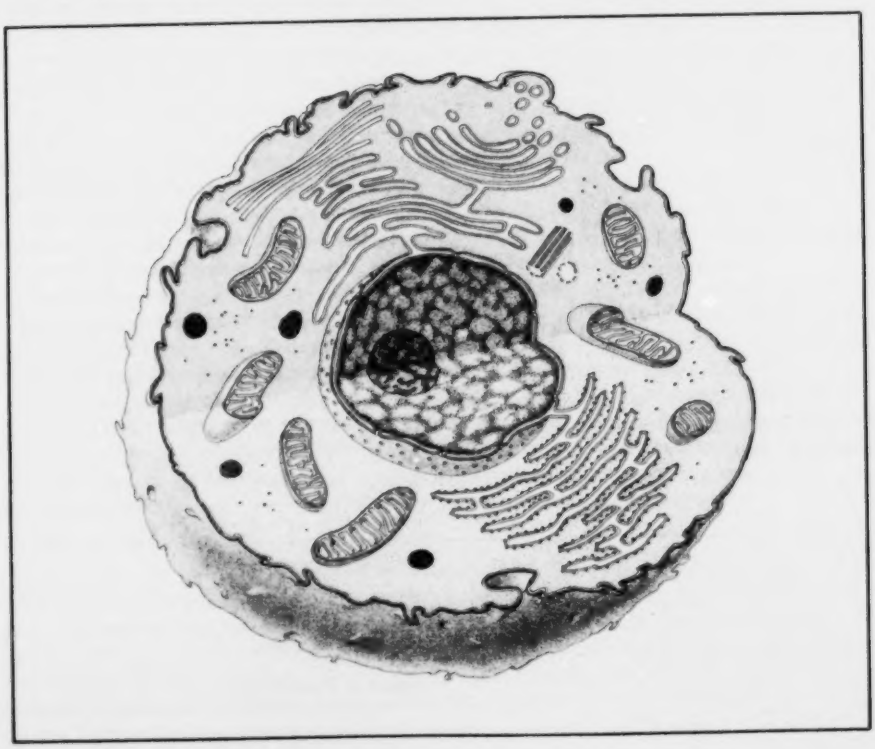
Program Highlights

Ten new BRDG awards were made in 1980, with new and continuation awards totaling $2,841,787. Twelve BRDG awards were completed after the approved 3 years of support, with 8 of the 12 original grantees qualifying for BRSG support.

The BRSG Program awarded grants to 506 institutions in FY 1980. The average grant amount was $88,271; the range was from $13,449 to $189,787. A program guide published in 1980 provides a list of FY 1980 BRSG grantees.

Through these awards, the BRSG Program directly supported approximately 10,000 research projects. The program indirectly supported an undetermined number of projects via BRSG-funded, centrally shared equipment, resources, and facilities. The following research highlights demonstrate the diverse uses made of BRSG awards by research institutions.

Toxic Serum Factor Found in Reye's Syndrome. A serum bioassay developed as a result of a BRSG-supported pilot study may aid diagnosis of Reye's syndrome (RS), a serious disease of children, which at present is difficult to identify. RS usually strikes suddenly after a child has recovered from influenza or chickenpox and is characterized by swelling of the brain and fatty degeneration of the liver. The new bioassay detects a factor in the blood of RS victims that interferes with the proper functioning of mitochondria, the cell's energy factories. Working in collaboration with a BRP-supported mass spectrometry facility, researchers are trying to identify the factor using a combination of gas chromatography and mass spectrometry. If the factor is found to be specific for RS, it



The BRSG Program supported 10,000 pilot and regular research projects in FY 1980. One pilot project resulted in development of a serum bioassay that may lead to improved diagnosis of Reye's syndrome (RS), a serious children's disease. In RS, the mitochondria, or sausage-shaped structures seen in this open view of the mammalian cell, are destroyed.

A BRSG-supported study by researchers (above) indicates that essential fatty acid (EFA) deficiency can profoundly retard growth. Current research seeks to correlate EFA deficiency with established biological events in the growth process.

might provide a basis for an in vitro diagnostic and prognostic test.

Immunization Against Chemical Carcinogens Tested. A potential vaccine against a class of environmental carcinogens, the polycyclic aromatic hydrocarbons (PAH's), is being tested as a result of BRSG-supported pilot research. PAH's are present in such substances as cigarette smoke, automobile exhaust, and charcoal-broiled food. The researchers developed an antigen compound from a noncarcinogen of the PAH class. When injected into mice, it stimulated production of antibodies that reacted with carcinogenic PAH's. In a study to determine whether this immunization with the antigen complex would protect against tumors, PAH carcinogen was applied externally to immunized and nonimmunized mice. Although the study is incomplete, the initial results indicate that the immunized mice were protected against tumors, but the control group was not. According to the researchers, immunization may be one means of preventing cancer induced by a particular class of chemicals.

Macrophages Produce Interferon. Production of human interferon by macrophages was accomplished at a BRSG grantee institution in FY 1980. In eight separate experiments in the BRSG pilot study, a macrophage preparation exposed to live influenza A virus produced interferon of the type detected in the blood of influenza patients in amounts of 100 to 800 units of interferon per milliliter. The results indicate a mechanism by which macrophages, which appear to have a central role in immune response and immune regulation, may contribute to the body's primary defenses against viral diseases and possibly against cancer. During the last 5 years, a number of clinical trials with

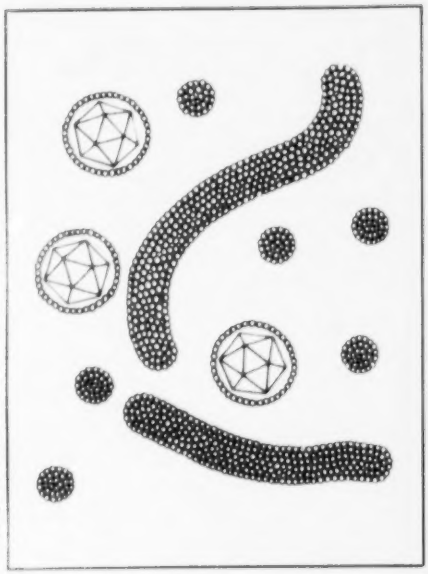
Photo by Bradford F. Hamm

A potential vaccine against a class of environmental carcinogens, the polycyclic aromatic hydrocarbons (PAH's) is being tested as a result of BRSG-supported pilot research. Initial findings have demonstrated protection against tumors in vaccinated mice.

exogenous human interferon have indicated it is effective against such viral infections as chickenpox, shingles, and herpes keratitis, as well as against osteogenic sarcoma and several other forms of cancer.

Essential Fatty Acid Deficiency Can Retard Growth. Essential fatty acid (EFA) deficiency can profoundly retard growth, according to a recent BRSG-supported pilot study. The research findings demonstrated that mice born to mothers who had been on a totally EFA-deficient diet throughout pregnancy were EFA-deficient at birth and achieved only 45 percent of normal body weight and 77 percent of normal brain weight at age 6 weeks. There was a delay in brain development of 7 days, which corresponds to 7 months in the human infant. Further research will attempt to correlate EFA deficiency with established biological events in the growth process. Investigators suspect that deficiency adversely affects the myelin, a complex molecular "sandwich" of fats and proteins that surrounds the nerve axons and insulates the nervous system. The research offers a plausible explanation of retarded growth in the central nervous system due to lack of essential fatty acids.

Low-Gold Alloys Found Useful for Tooth Fillings. With the dramatic rise in the price of gold, dentists and dental laboratories have made increasing use of filling alloys with lower gold content than the 70 to 80 percent previously used. Supplemental BRSG support of ongoing dental research at one center enabled investigators to study the effect of certain filling alloys in patients over a 3-year period. Use of the new alloys, combinations of silver, copper, or palladium with gold, indicated that gold content can be

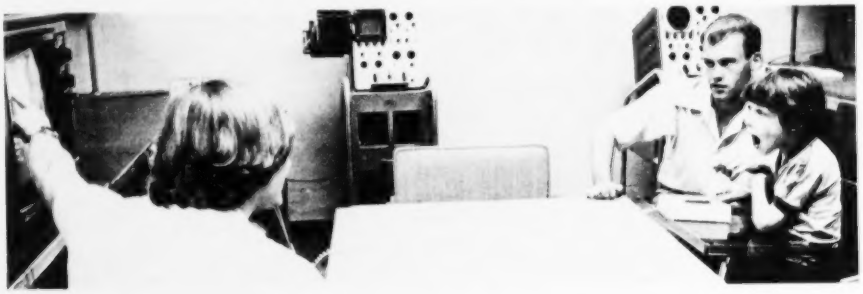


From Viral Hepatitis by Melnick, J. L. Dreesman, G. R. Holinger, F.B. Copyright 1977 by Scientific American, Inc. All rights Reserved

In the 1980's more researchers will seek BRSG funds to complement their research project grants. These funds will enable them to investigate physiological processes, viruses (such as the hepatitis B virus above), and other life forms, to prevent, diagnose, and treat human disease.

reduced to 42 percent with no reduction in resistance to tarnish or corrosion.

Potential Vaccine Developed Against Infectious Mononucleosis. Pilot studies supported with BRSG funds have led to development of a vaccine that may protect against infectious mononucleosis and certain types of human cancer. Infectious mononucleosis, one of the most common diseases in the United States, is caused by the Epstein-Barr virus, which may also be a cofactor in the development of two types of cancer, Burkitt's lymphoma and nasopharyngeal carcinoma. Researchers stimulated production of antibodies against Epstein-Barr virus by vaccinating an animal with membrane antigens from a cell line infected with the virus. Encouraged by these pilot studies, investigators have undertaken to develop methods for harvesting the antigens in quantities large enough to make a practical vaccine against the virus.



Boy with cerebral palsy uses guttural sounds to activate word indicator on the electronic verbalizer machine. Partially supported by BRSG funds, the machine (above right) has an almost unlimited word capacity and enables children who cannot speak to communicate.

Laryngeal Photography Helps Therapists Teach the Hearing Impaired to Speak More Naturally. A BRSG award enabled one institution to purchase an image-processing system to automate analysis of ultra-high-speed laryngeal films (5,000 frames per second), a procedure previously performed by hand. The studies contribute data relevant to a theory of vocal cord motion and to development of aids to teach speech to the hearing impaired. Although high-speed laryngeal photography has been used in speech research for 40 years, it is estimated that no more than 5 minutes of utterances had been analyzed in detail before purchase of the specialized equipment.

Verbalizer Gives "Speech" to Those Who Cannot Talk. Because they are nonverbal, many victims of muscular dystrophy, multiple sclerosis, cerebral palsy, speech defects, and accidents are often thought to be retarded even though their intellects are normal or above normal. Tailoring a recently developed electronic verbalizer machine to their unique handicaps will enable them to communicate better and dispel this false impression. Over the past 5 years, the electronic verbalizer machine, partially supported by BRSG funds, has evolved from a primitive screen of printed words to a computerized scanner system. Words that can be formed into sentences appear on a color television monitor when buttons or switches are activated. The machine has been used by several handicapped persons. The latest model was custom designed for a 14-year-old boy with cerebral palsy. It holds 1,300 words related to several subject areas, but has an unlimited word capacity. In the past, he laboriously pointed to words on a board attached to his wheelchair, taking almost a minute to communicate a six-word message. Now he uses a screen indicator that quickly scans a list of words on the verbalizer screen. The indicator can be triggered by a manual switch or by a voice-activated device that detects any gutteral sound made into a microphone. The vocal control was added because the boy's shoulder tremors made it difficult for him to use the switch.

Future Program Directions

Rhesus infant and its mother (opposite) at a regional primate research center. The DRR supports 7 primate centers and a variety of other animal, clinical, and biotechnology resource facilities.

The current climate of increasing research costs and limited budgets for funding research will continue to heighten the demand for BRSG funds. More researchers will seek these funds from their institutions to complement or supplement their research grants. Thus, a top program priority in the 1980's will be to strengthen the BRSG Program by increasing the BRSG budget from 2.1 percent to 3.1 percent and ultimately to 4 percent of the total NIH research grants appropriation. A national panel of consultants recommended in 1975 that the minimum level should be 3.7 percent.

A new shared-instrument grant program will be initiated to respond selectively to the biomedical research equipment needs of grantee institutions. To qualify for funding, the instrument will have to be sufficiently costly and useful to a large enough group of users to justify national peer review and central funding decisions.

Finally, the program plans to revise the grant computation formula to achieve the allocation pattern agreed to in 1976; to reassess grantee eligibility; to reexamine the types of research grants used to compute BRSG awards; and to consider means to evaluate the program.

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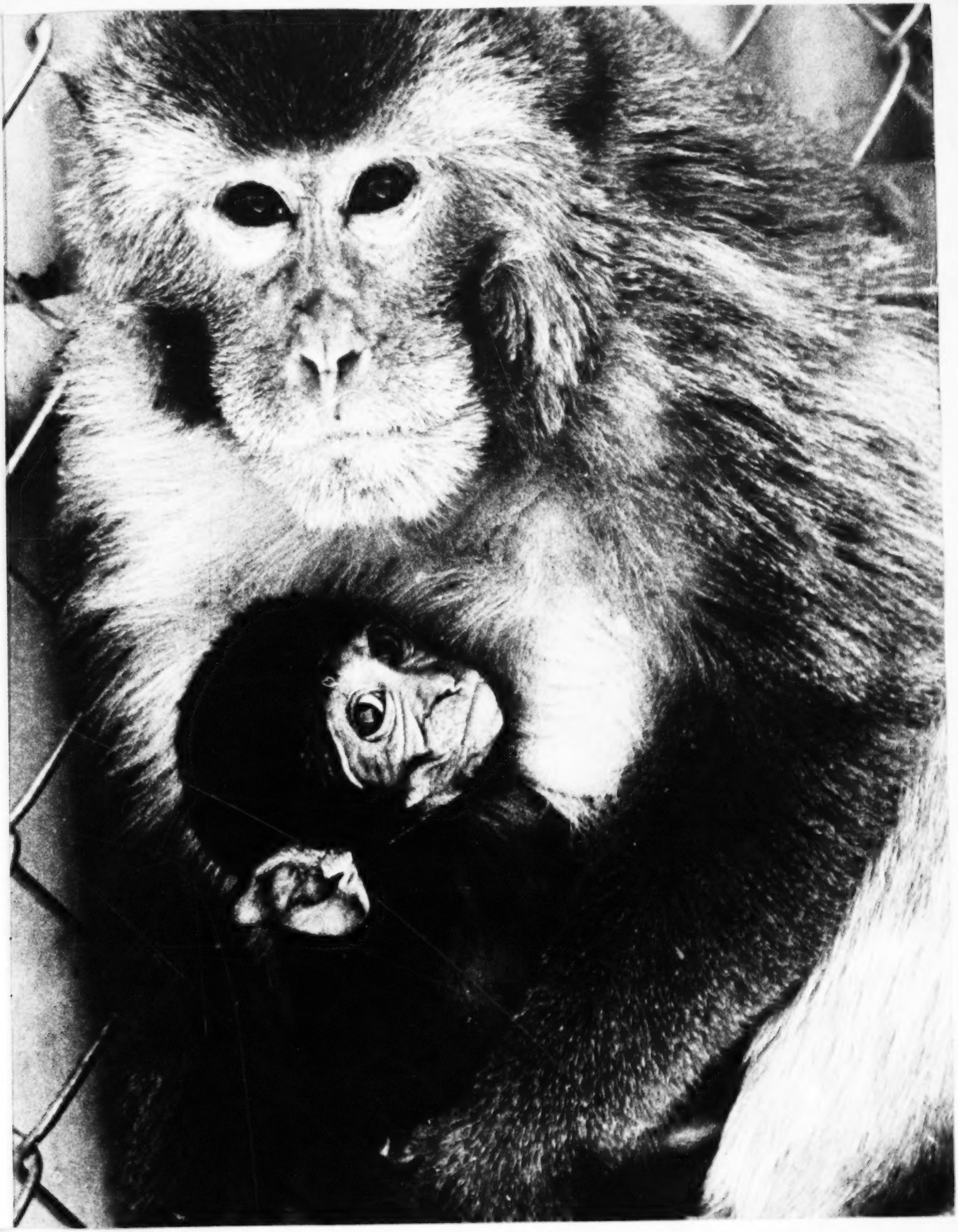

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